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(54) Titre : FORMES GALENIQUES RESISTANTES A LA RUPTURE A LIBERATION RETARDEE
(54) Title: BREAK-RESISTANT DELAYED-RELEASE FORMS OF ADMINISTRATION

(57) Abrégé/Abstract:
The invention relates to a form of administration comprising a physiologically effective substance (A); one or several optional physiologically acceptable adjuvants (B); a synthetic or natural polymer (C); and an optional natural, semisynthetic, or synthetic wax (D). Said form of administration is provided with a minimum breaking strength of 400 N while releasing the physiologically effective substance (A) at least partly in a delayed manner in physiological conditions.

Abstract

The invention relates to a form of administration comprising a physiologically effective substance (A); one or several optional physiologically acceptable adjuvants (B); a synthetic or natural polymer (C); and an optional natural, semisynthetic, or synthetic wax (D). Said form of administration is provided with a minimum breaking strength of 400 N while releasing the physiologically effective substance (A) at least partly in a delayed manner in physiological conditions.

Break-resistant delayed release forms of administration

The present invention relates to a form of administration for administering a physiologically active substance (A), wherein the form of administration is mechanically stabilised, so that it cannot be comminuted with conventional methods, such as pounding, crushing, grinding in a mortar, etc, or at least can only be comminuted with great difficulty. The substance (A) is released from the form of administration according to the invention under physiological conditions with an at least partially delayed profile.

Numerous physiologically active substances, such as nutritional supplements, therapeutic agents, etc are produced as delayed-release formulations, ie, unlike the case with conventional formulations (eg so-called "*immediate release*" formulations), the release of the substances from these formulations into the organism is delayed for a comparatively long period, often amounting to several hours. The release of the substance from the form of administration on the one hand and metabolisation or excretion by the organism on the other, ensure a relatively uniform blood plasma level for the administered substance. As a consequence of this, it is frequently possible to reduce the number of dose units to be taken per day by patients, often, intake is only required once or twice a day.

In certain cases, delayed-release formulations may also reduce the extent of the side effects of the substance. For example, some therapeutic agents result in intensified side effects if a specific concentration limit of the therapeutic agent is exceeded, at least transiently. Such therapeutic agents are, therefore, to a large extent, unsuitable for "*immediate release*" formulations, in particular if administration only two or three times daily is desirable. Medicinal agents of this kind therefore are usually administered as delayed-release formulations, whereby the continuous release of the active substance is ensured and the short-term occurrence of elevated concentrations is avoided.

In the case of delayed-release formulations, the physiologically active substance is usually either embedded in a matrix that controls release, and/or the form of administration is coated with a film that controls release.

However, elderly patients in particular frequently have difficulties taking solid forms of administration, such as tablets, gelatin capsules, etc. They choke on them and sometimes develop pronounced aversions to such forms of administration.

To counter this, various types of apparatus have been developed by means of which solid forms of administration can be comminuted or pulverised ("*tablet crusher*"). This type of apparatus is used, for example, by the care staff in old people's homes. The forms of administration are then given to the people requiring care not as tablets etc, but as powder, in order, for example, to avoid the problems with swallowing tablets.

However, the comminution of forms of administration with apparatus of this type is problematic if the forms of administration are delayed-release formulations. To be precise, comminution generally results in the destruction of the inner structure of the form of administration, which is responsible for the delayed release, thus cancelling out the delayed-release action. As a result of the comminution, the diffusion paths of the constituent physiologically active substances are shortened and/or the diffusion barriers removed. For example, after comminution, a delayed-release formulation in which the delayed release is to be achieved by means of a film coating only retains the film coating on a small percentage of its solid surface. As a consequence of this, after administration, frequently the entire amount of the physiologically active substance originally contained in the form of administration is released in a relatively short time, whereby a comparatively very high plasma concentration of the substance is achieved for a relatively short time. In this way, the original delayed-release formulations become "*immediate release*" formulations.

However, depending upon the physiological effectiveness of the substance, this may cause considerable side effects, in extreme cases even the death of the patient. Examples of substances with a hazard potential of this type include anti-parkinson drugs, antiepileptics, antidiabetics, antihypertensive agents, antiarrhythmics, etc.

As a rule, the people who comminute the forms of administration for themselves or for others are not aware of these risks. Deaths of patients are known which are probably attributable to the pulverisation of delayed-release formulations by nurses or carers. For further details, reference is made for example to JE Mitchell, *Oral Dosage Forms That Should Not Be*

Crushed: 2000 Update. Hospital Pharmacy, 2000; H Miller et al., *To Crush or Not to Crush*, Nursing 2000; R Grittith et al., *Tablet Crushing and the law: the implications for nursing*; Prof Nurse 2003; JG Schier et al, *Fatality from administration of labetalol and crushed extended-release nifedipine*, Ann Pharmacotherapy 2003; A James, *The legal and clinical implications of crushing tablet medication*, Nurse Times 2005, 100(50), 28-9; and P Cornish, *"Avoid the Crush": hazards of medication administration in patients with dysphagia or a feeding tube*, CMAJ 2005, 172(7), 871-2.

Delayed-release formulations can also create problems with small children. For example, children are often unable to distinguish solid forms of administration from sweets. If children find such forms of administration, for example because their parents have carelessly left them lying around in the home, there is a risk that the children may think the forms of administration are sweets, put them in their mouths and chew them. If this involves delayed-release formulations containing a therapeutic agent in a dose intended for adults, in such a case, the child is already at risk of an overdose due to the larger content of therapeutic agent. Chewing the form of administration and the associated cancellation of the delayed-release action intensifies this risk still further, since the already excessive dose is also released in a greatly reduced period of time, which would entail considerable risks even for an adult but could have consequences that are even more drastic for a child.

Chewing delayed-release formulations can also lead to an overdose of the substance contained therein in adults. For example, adults sometimes chew the forms of administration quite deliberately, since, often in ignorance of the type and purpose of a delayed-release formulation, they hope this will achieve a quicker effect.

A known possibility for reducing the risks resulting from the comminution of delayed-release formulations is to add antagonists, ie antidotes or compounds which produce physiological defence reactions, to the form of administration, wherein the physiological action of these additives is, if possible, only activated if the form of administration has been comminuted before administration. However, this method has the drawback that the physiologically active substance is nonetheless administered in non-delayed form and that the organism is additionally exposed to another physiologically active substance, for example an antidote, or that a defence reaction, such as vomiting, for example, is triggered.

There is, therefore, a requirement for pharmaceutical forms of administration with delayed release that reduce the risk of overdose so that there is no need for antidotes, etc.

The invention is based on the object of providing a form of administration having advantages over the forms of administration in the prior art. The form of administration should release a physiologically active substance with delayed release but reduce the risk of overdose, in particular as the consequence of improper handling of the form of administration, such as chewing, crushing, grinding in a mortar, etc.

It was surprisingly found that this object is achieved by a form of administration comprising

- a physiologically active substance (A) (= component (A))
- optionally one or a plurality of physiologically compatible excipients (B) (= component (B)),
- a synthetic or natural polymer (C) (= component (C)) and
- optionally a natural, semi-synthetic or synthetic wax (D) (= component (D)),

wherein the form of administration has a resistance to breaking of at least 400 N, preferably at least 420 N, more preferably at least 440 N, still more preferably at least 460 N, most preferably at least 480 N and in particular at least 500 N and, under physiological conditions, the physiologically active substance (A) is at least partially delayed. Consequently, the form of administration according to the invention comprises a physiologically active substance (A) with at least partially delayed release.

The form of administration according to the invention exhibits mechanical strength over a wide temperature range, in addition to the resistance to breaking, optionally also sufficient hardness and impact strength, so that it is virtually impossible for it to be comminuted or pulverised by chewing, grinding in a mortar, pounding, etc. and also by means of commercially available apparatus for the pulverisation of conventional forms of administration. In this regard, this is not necessarily achieved by the hardness of the form of administration. For example, in particular its impact strength may have the result that, although it may be deformed due to an external mechanical action, for example by means of a hammer, it does not disintegrate into numerous fragments. Comminution is not even successful if the form of administration is first chilled to increase its brittleness, for example to temperatures below -25°C, -40°C or even in liquid nitrogen.

As a consequence of this, delayed release is retained and an overdose due to incorrect handling of the form of administration is effectively prevented.

The advantageous properties of the forms of administration according to the invention, in particular also their mechanical properties, cannot be automatically achieved by processing the components (A), (C), optionally (B) and optionally (D) by means of any conventional methods for the production of forms of administration. Instead, it is usually necessary to select suitable types of apparatus for production and set suitable parameters, in particular pressure/force, temperature and time. It is only when the components are exposed to a sufficient pressure at a sufficient temperature for a sufficient period during production that forms of administration with the desired properties are obtained. Therefore, even if conventional types of apparatus are used, it is usually necessary to adapt the production protocols in order to meet the required criteria.

Delayed release according to the invention should preferably be understood to mean a release profile in which the physiologically active substance is released over a lengthy period with a reduced intake frequency with the object of an extended therapeutic action. In particular, this is achieved with peroral administration. The expression "with at least partially delayed release" covers according to the invention all forms of administration which ensure modified release of the physiologically active substances contained therein. The forms of administration are preferably coated or uncoated forms of administration that are produced with special excipients, with particular methods or by a combination of both options in order purposefully to change the release rate or the location of the release.

The time profile of the release with the forms of administration according to the invention includes the following types: extended release, delayed release, repeat action release, prolonged release and sustained release.

For the purposes of the description, "delayed release" preferably means the delayed release of the physiologically active substance for a defined finite time (*lag time*) after which release takes place unhindered. "Repeat action release" preferably defines the initial release of a first portion of the physiologically active substance followed by at least one further portion that is released following this. "Prolonged release" preferably defines release at a reduced rate in

order to maintain therapeutic efficacy, reduce toxic effects or for other therapeutic reasons. "Sustained prolonged release" preferably defines a continuous release over a relatively long period in order to reduce the frequency of administration. For further details, reference is made for example, to KH Bauer, Lehrbuch der Pharmazeutischen Technologie, 6th Edition, WVG Stuttgart, 1999 and the European Pharmacopoeia.

In a preferred embodiment, under physiological conditions, after 5 hours, the form of administration according to the invention has released at the most 99%, more preferably at the most 90%, more preferably at the most 75%, still more preferably at the most 50%, most preferably at the most 40% and in particular at the most 30% of the substance (A). In this regard, it is particularly preferable for the form of administration in this case to contain neither tramadol hydrochloride, nor oxycodone hydrochloride, more preferably no opioid [N02A] (for the meaning of "N02A" see below). The release is in this regard preferably determined using the standardised method in the European Pharmacopoeia, preferably under the conditions described in example 1.

Preferably, under physiological conditions, the form of administration according to the invention releases the physiologically active substance (A) as follows: 0.1 to 75 % by weight after 30 minutes, 0.5 to 95 % by weight after 240 minutes, 1.0 to 100 % by weight after 480 minutes and 2.5 to 100 % by weight after 720 minutes.

Further preferred release profiles 1 to 5 are summarised in the following table [data in % by weight of released component (A)]:

Time [h]	No 1	No 2	No 3	No 4	No 5
1	0-30	0-50	0-50	15-25	20-50
2	0-40	0-75	0-75	25-35	40-75
4	3-55	3-95	10-95	30-45	60-95
8	10-65	10-100	35-100	40-60	80-100
12	20-75	20-100	55-100	55-70	90-100
16	30-88	30-100	70-100	60-75	
24	50-100	50-100	>90		
36	>80	>80			

Preferably, the release behaviour of the form of administration according to the invention is largely independent of the pH value of the release medium, that is, the release profile in

artificial intestinal juice preferably corresponds substantially to the release profile in artificial gastric juice. Preferably, at any time during the measurement, the deviation of the two release profiles from each other is at the most 20%, more preferably at the most 15%, still more preferably at the most 10%, still more preferably at the most 7.5%, most preferably at the most 5.0% and in particular at the most 2.5%.

Preferably, the form of administration according to the invention has uniform release behaviour. In this regard, preferably, the release behaviour of the physiologically active substance (A) is interindividually uniform (that is compared to the forms of administration produced using the same method) and/or uniform within a single form of administration (that is compared to partial segments of the same form of administration). Preferably, in a comparison of this kind of two samples each with a mass of preferably 500 mg, at any time of the measurement, the total amounts of the released active substance deviate from each other by at the most 20%, more preferably at the most 15%, still more preferably at the most 10%, still more preferably by at the most 7.5%, most preferably at the most 5.0% and in particular by at the most 2.5%.

Preferably, the release profile of the form of administration according to the invention is stable in storage, preferably in storage at a high temperature, eg at 37°C, for 3 months in sealed containers. In this context, "stable in storage" means that, in a comparison of the initial release profile with the release profile after storage, the two release profiles deviated from each other by at the most 20%, more preferably by at the most 15%, still more preferably by at the most 10%, still more preferably by at the most 7.5%, most preferably by at the most 5.0% and in particular by at the most 2.5%.

By the use of certain polymers, in suitable quantities and under suitable conditions it is achieved according to the invention that the form of administration has a resistance to breaking of at least 400 N, preferably at least 420 N, more preferably at least 440 N, still more preferably at least 460 N, most preferably 480 N and in particular at least 500 N (measured as specified in the description; the preferred method for the determination of the resistance to breaking according to the invention is a modification of the method "*Resistance to Crushing of Tablets*" described in the European Pharmacopoeia 5,0 on page 235, 2.9.8). This enables comminution, eg pulverisation of the form of administration with conventional means, to be effectively prevented.

According to the invention, comminution should be understood to mean the pulverisation of the form of administration under the application of force with conventional means, such as, for example, a mortar and pestle, hammer, mallet or other usual means for pulverisation, in particular also devices specially developed for this purpose (*tablet crushers*), wherein any fines that may occur (particle size equal to or smaller than 0.3 mm) must not exceed 5 % by weight.

The form of administration according to the invention is therefore suitable for preventing an overdose of physiologically active substances, in particular of nutritional supplements and therapeutic agents, which are provided in delayed-release formulations. In this regard, it is possible to dispense with antidotes, irritants, etc. In addition to preventing overdoses and the accompanying risks for patients, the forms of administration according to the invention also ensure that the other advantages of the delayed-release formulation, such as for example uniform release over a lengthy period are retained and cannot be easily cancelled out.

To achieve the necessary resistance to breaking of the form of administration according to the invention, at least one synthetic or natural polymer (C) is used, which contributes considerably to the increased resistance to breaking of the form of administration. The resistance to breaking of the form of administration is at least 400 N, preferably at least 420 N, more preferably at least 440 N, still more preferably at least 460 N, most preferably at least 480 N and in particular at least 500 N, wherein the resistance to breaking is determined according to method specified in the description. In a preferred embodiment, the resistance to breaking of the form of administration is at least 500 N, more preferably at least 600 N, more preferably at least 700 N, still more preferably at least 800 N, still more preferably at least 900 N, most preferably at least 1000 N and in particular at least 1100 N.

In addition to its resistance to breaking, the form of administration according to the invention is preferably also characterised by further mechanical properties, for example its hardness, impact resistance, impact elasticity and/or its modulus of elasticity, optionally also at low temperatures (eg below -24°C, below -40°C or in liquid nitrogen).

In a preferred embodiment, the form of administration according to the invention has a density of at least 0,80 or at least 0.85 g/cm^3, more preferably at least 0.90 or at least 0.95

g/cm^3, still more preferably at least 1.00, at least 1.05 or at least 1.10 g/cm^3, most preferably in the region of 0.80 to 1.35 g/cm^3 and in particular in the region of 0.95 to 1.25 g/cm^3.

The form of administration according to the invention is characterised by a comparatively homogeneous distribution of density. Preferably, the densities of two partial segments of the form of administration each with a volume of 1.0 mm^3 deviate from each other by at the most ±10%, more preferably by at the most ±7.5%, still more preferably by at the most ±5.0%, most preferably by at the most ±2.5% and in particular by at the most ±1.0%.

The form of administration according to the invention is characterised by a comparatively homogeneous distribution of the physiologically active substance (A). Preferably, the content of component (A) in two partial segments of the form of administration each with a volume 1.0 mm^3 deviate from each other by at the most ±10%, more preferably by at the most ±7.5%, still more preferably by at the most ±5.0%, most preferably by at the most ±2.5% and in particular by at the most ±1.0%.

The total weight of the form of administration according to the invention is preferably in region of 0.01 g to 1.5 g, more preferably of 0.05 g to 1.2 g, more preferably of 0.1 g to 1.0 g, most preferably of 0.2 g to 0.9 g and in particular of 0.25 g to 0.8 g.

Preferably, the form of administration according to the invention comprises at least one polymer (C) selected from the group consisting of polyalkylene oxide, preferably polymethylene oxide, polyethylene oxide, polypropylene oxide; polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, poly(hydroxy fatty acids), such as, for example, poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (Biopol®), poly(hydroxyvaleric acid), polycaprolactone, polyvinyl alcohol, polyesteramide, polyethylene succinate, polylactone, polyglycolide, polyurethane, polyvinylpyrrolidone, polyamide, polylactide, polyacetal (for example polysaccharides optionally with modified side chains), polylactid/glycolide, polylactone, polyglycolide, polyorthoester, polyanhydride, block polymers of polyethylene glycol and polybutylene terephthalate (Polyactive®), polyanhydride (Polifeprosan), the copolymers thereof and mixtures of at least two of the polymers named.

High-molecular, thermoplastic polyalkylene oxides, in particular polyethylene oxide, polypropylene oxide or (block) copolymers thereof are preferred. Particularly preferred are

high-molecular polyalkylene oxides, in particular polyethylene oxides, with a preferably weight average molecular weight (M_w) or viscosity average molecular weight ($M_□$) of at least 0.5 10^6 g/mol, preferably at least 1.0 10^6 g/mol, more preferably at least 2.5 10^6 g/mol, still more preferably at least 5.0 10^6 g/mol, most preferably at least 7.5 10^5 g/mol or 7.5 10^6 g/mol and in particular at least 10 10^6 g/mol, preferably 1.0 10^6 to 15 10^6 g/mol. The person skilled in the art knows suitable methods for the determination of M_w or $M_□$. Preferably, $M_□$ is determined by rheological measurements and M_w is determined by gel permeation chromatography (GPC) on suitable phases.

The polymers (C) preferably have a viscosity at 25 °C of 4,500 to 17,600 mPa/s (cP), measured in a 5 % by weight aqueous solution using a Brookfield viscosimeter, Model RVF (spindle No 2 / rotational speed 2 rpm), of 400 to 4,000 mPa/s (cP), measured on a 2 % by weight aqueous solution using said viscosimeter (spindle No 1 or 3 / rotational speed 10 rpm) or of 1,650 to 10,000 mPa/s (cP), measured on a 1 % by weight aqueous solution using said viscosimeter (spindle No 2 / rotational speed 2 rpm).

The polymer (C) is preferably used as a powder. It may be soluble in water.

Preferably, the polymer (C) is used in a quantity of at least 20 % by weight, more preferably at least 30 % by weight, still more preferably at least 40 % by weight, most preferably at least 50 % by weight, and in particular at least 60 % by weight, based on the total weight of the form of administration. In a preferred embodiment, the quantity is in the region 20 to 49 % by weight, based on the total weight of the form of administration.

The form of administration according to the invention is suitable for the administration of a plurality of physiologically active substances (A) in one form of administration. Preferably, the form of administration contains only one specific physiologically active substance (A), preferably a nutritional supplement or a therapeutic agent (= active pharmaceutical ingredient).

The percentage by weight of the physiologically active substance (A) based on the total weight of the form of administration according to the invention is preferably in the region of 0.01 to 95 % by weight, more preferably 0.5 to 80 % by weight, still more preferably 1.0 to 70

% by weight, most preferably 5.0 to 60 % by weight and in particular 10 to 50 % by weight. In a preferred embodiment, the percentage by weight is more than 20 % by weight.

In a preferred embodiment of the form of administration according to the invention, it does not contain any psychotropically active substance. The person skilled in the art knows which substances have a psychotropic action. Substances that influence psychological processes commonly have a psychotropic action, ie a specific action on psychological functions. Thus, substances with a psychotropic action can influence moods, either raising them or lowering them. For the purposes of the description, substances with a psychotropic action include in particular opioids, stimulants, tranquillisers (barbiturates and benzodiazepines) and further narcotics. Preferably, substances with a psychotropic action are substances which, in particular when improperly administered (in particular with the intention of abuse) cause an accelerated increase in active ingredient levels compared to proper oral administration giving the abuser the desired effect, namely the "kick". This kick can be achieved for example if the powdered form of administration is administered nasally, ie sniffed. Preferably, substances with a psychotropic action are substances which (in the appropriate dose, form of administration and type of administration) influence human mental activity and/or sensory perception in such a way that they are in principle suitable for abuse.

The following opiates, opioids, tranquillisers or other narcotics are substances with a psychotropic action and according to the invention therefore are preferably not contained in the form of administration: alfentanil, allobarbital, allylprodine, alphaprodine, alprazolam, amfepramone, amphetamine, amphetaminil, amobarbital, anileridine, apocodeine, barbital, bemidone, benzylmorphine, bezitramide, bromazepam, brotizolam, buprenorphine, butobarbital, butorphanol, camazepam, carfentanil, cathine/ D-norpseudoephedrine, chlordiazepoxide, clobazam, clofedanol, clonazepam, clonitazene, clorazepate, clotiazepam, cloxazolam, cocaine, codeine, cyclobarbital, cyclorphan, cyprenorphine, delorazepam, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphone, diazepam, dihydrocodeine, dihydromorphine, dihydromorphone, dimenoxadol, dimephetamol, dimethylthiambutene, dioxaphetylbutyrate, dipipanone, dronabinol, eptazocine, estazolam, ethoheptazine, ethylmethylthiambutene, ethyl loflazepate, ethylmorphine, etonitazene, etorphine, fencamfamine, fenethylline, fenpipramide, fenproporex, *fentanyl*, fludiazepam, flunitrazepam, flurazepam, halazepam, haloxazolam, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, hydroxymethyl-

morphinan, ketazolam, ketobemidone, levacetylmethadol (LAAM), levomethadone, levorphanol, levophenacylmorphane, levoxemacin, lofentanil, loprazolam, lorazepam, lormetazepam, mazindol, medazepam, mefenorex, meperidine, meprobamate, metapon, meptazinol, metazocine, methylmorphine, metamphetamine, methadone, methaqualone, 3-methylfentanyl, 4-methylfentanyl, methylphenidate, methylphenobarbital, methyprylon, metopon, midazolam, modafinil, morphine, myrophine, nabilone, nalbuphene, nalorphine, narceine, nicomorphine, nimetazepam, nitrazepam, nordazepam, norlevorphanol, normethadone, normorphine, norpipanone, opium, oxazepam, oxazolam, oxycodone, oxymorphone, Papaver somniferum, Papaveretum, pernoline, pentazocine, pentobarbital, pethidine, phenadoxone, phenomorphane, phenazocine, phenoperidine, piminodine, pholcodeine, phenmetrazine, phenobarbital, phentermine, pinazepam, pipradrol, piritramide, prazepam, profadol, proheptazine, promedol, properidine, propoxyphene, remifentanil, secbutabarbital, secobarbital, sufentanil, temazepam, tetrazepam, tilidine (cis and trans), tramadol, triazolam, binylbital, N-(1-methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamide, (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (1R, 2R, 4S)-2-(dimethylamino)methyl-4-(p-fluorbenzyloxy)-1-(m-methoxyphenyl)cyclohexanol, (1R, 2R)-3-(2-dimethylaminomethyl-cyclohexyl)-phenol, (1S, 2S)-3(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (2R, 3R)-1-dimethylamino-3(3-methoxy-phenyl)-2-methyl-pentan-3-ol, (1RS, 3RS, 6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol, preferably as racemate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl 2-(4-isobutyl-phenyl)-propionate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)-propionate, 3-(2-Dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionate, (RR-SS)-2-acetoxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-trifluoromethyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-4-chloro-2-hydroxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methyl-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methoxy-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl-ester, (RR-SS)-2-hydroxy-5-nitro-benzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2',4'-difluoro-3-hydroxy-biphenyl-4-carboxylic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester and corresponding stereoisomeric compounds, in each case the corresponding derivatives thereof, physiologically compatible

enantiomers, stereoisomers, diastereomers and racemates and the physiologically compatible derivatives thereof, for example ethers, esters or amides, and in each case the physiologically compatible compounds thereof, in particular the salts and solvates thereof, for example hydrochloride.

In particular, the form of administration according to the invention preferably does not contain any substance selected from the group consisting of opioids [A07DA, N01AH, N02A, R05DA, R05FA,], barbiturates [N01AF, N01AG, N03AA], benzodiazepine derivatives [N03AE], agents for the treatment of opiate dependence [N07BC], anxiolytics [N05B], hypnotics and sedatives [N05C], psychostimulants, agents for the treatment of attention deficit/hyperactivity disorder (ADHD) and nootropics [N06B], antiemetics [A04A], antiobesity preparations excluding diet products [A08A], centrally acting muscle relaxants [M03B] and antidotes [V03AB]. The references in brackets hereby correspond to the ATC Index, as used by the WHO for the classification of therapeutic agents (preferred version: January 2005 or 2006). With regard to further information on the ATC Index, reference is made for example to U Fricke, J Günther, Anatomisch-therapeutisch-chemische Klassifikation mit Tagesdosen für den deutschen Arzneimittelmarkt: Methodik der ATC-Klassifikation und DDD-Festlegung. ATC-Index mit DDD-Angaben, Wissenschaftliches Institut der AOK and Swiss Pharmaceutical Society, Index Nominum: International Drug Directory, CRC Press; 18th edition (January 31, 2004).

In a preferred embodiment, the form of administration according to the invention does not contain any compound selected from the group consisting of

(1) analgesics, such as, for example, aspirin, acetaminophen, deflunisal, etc,

(2) anaesthetics, such as, for example, lidocaine, procaine, benzocaine, xylocaine, etc,

(3) antiarthritiics and anti-inflammatory agents, such as, for example, phenylbutazone, indomethacin, sulindac, dexamethasone, ibuprofen, allopurinol, oxyphenbutazone probenecid, cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, triamcinolone, indomethacin, sulindac and the salts thereof and corresponding sulfides, etc,

(4) antiasthma drugs, such as, for example, theophylline, ephedrine, beclomethasone dipropionate, epinephrine, etc,

(5) urinary tract disinfectives, such as, for example, sulfarmethoxazole, trimethoprim, nitrofurantoin, norfloxicin, etc,

(6) anticoagulants, such as, for example, heparin, bishydroxy coumarin, warfarin, etc,

(7) anticonvulsants, such as, for example, diphenylhydantoin, diazepam, etc,

(8) antidepressants, such as, for example, amitriptyline, chlordiazepoxide, perphenazine, protriptyline, imipramine, doxepin, etc,

(9) substances suitable for the treatment of diabetes and for the regulation of blood sugar, such as, for example, insulin, tolbutamide, tolazamide, somatotropin, acetohexamide, chlorpropamide, etc,

(10) antineoplastics, such as, for example, adriamycin, fluouracil, methotrexate, asparaginase, etc,

(11) antipsychotics, such as, for example, prochlorperazine, lithium carbonate, lithium citrate, thioridazine, molindone, fluphenazine, trifluoperazine, perphenazine, amitriptyline, triflupromazine, etc,

(12) antihypertensives, such as, for example, spironolactone, methyldopa, hydralazine, clonidine, chlorothiazide, deserpidine, timolol, propanolol, metaprotol, prazosin hydrochloride, reserpine, etc,

(13) muscle relaxants, such as, for example, mephalan, danbrolene, cyclobenzaprine, methocarbarnol, diazepam, succinoyl chloride, etc,

(14) antiprotozoals, such as, for example, chloramphenicol, chloroquine, trimethoprim and sulfamethoxazole,

(15) spermicidals, such as, for example, nonoxynol,

(16) antibacterial substances, such as, for example, beta-lactam antibiotics, tetracyclines, chloramphenicol, neomycin, cefoxitin, thienamycin, gramicidin, bacitracin, sulfonamides, aminoglycoside antibiotics, tobramycin, nitrofurazone, nalidixic acid and analogues and the antimicrobial combination of fludalanine/pentizidone,

(17) antihistamines and decongestants, such as, for example, perilamine, chlorpheniramine (eg chlorpheniramine maleate), tetrahydrozoline and antazoline,

(18) antiparasitic substances, such as, for example, ivermectin,

(19) antiviral substances, such as, for example, acyclovir and interferon,

(20) antifungal, amoebicidal, trichomonacidal agents or antiprotozoals, such as, for example, polyoxyethylene nonylphenol, alkylaryl sulfonate, oxyquinoline sulfate, miconazole nitrate, sulfanil amide, candicidin, sulfisoxazole, nysatidin, clotrimazole, metronidazol, etc, and

(21) losoxanthrone, theophylline or ß-hydroxyethyl-theophylline (etophylline), diphenhydramine or the hydrochloride thereof, diltiazem or the hydrochloride thereof and diphenylethyl(adenosine).

In a preferred embodiment, the form of administration according to the invention does not contain any substances which irritate the nasal passages and/or pharynx, that is substances which, when administered via the nasal passages and/or pharynx, bring about a physical reaction which is either so unpleasant for the patient that he/she is unwilling or unable to continue the administration, for example burning, or in a physiological way prevents the intake of the active ingredient, for example due to increased nasal secretion or sneezing. Further examples of substances which irritate the nasal passages and/or pharynx are substances which cause burning, itching, an urge to sneeze, increased secretions or a combination of at least two of these irritations. Corresponding substances and the conventionally used quantities thereof are known to the person skilled in the art. For example, some of the substances which irritate the nasal passages/or pharynx are based on one or more ingredients or one or more plant parts of a hot substance drug. Corresponding hot substance drugs are known per se to the person skilled in the art and are described, for example, in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof Dr Hildebert Wagner, 2nd revised edition, Gustav Fischer Verlag, Stuttgart-New York, 1982, pages 82 et seq. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

The form of administration according to the invention furthermore preferably does not contain any antagonists for the physiologically active substance (A), preferably no antagonists against psychotropic substances, in particular no antagonists against opioids. Suitable antagonists for a given physiologically active substance (A) are known to the person skilled in the art and can be present as such or in the form of corresponding derivatives thereof, in particular esters or ethers, or in each case in the form of corresponding physiologically compatible compounds, in particular in the form of the salts or solvates thereof. Preferably, the form of administration according to the invention does not contain any antagonists selected from the group comprising naloxone, naltrexone, nalmefene, nalide, nalmexone, nalorphine or naluphine, in each case optionally in the form of a corresponding physiologically compatible compound, in particular in the form of a base, a salt or solvates and no neuroleptics, eg a compound selected from the group comprising aloperidol, promethacine, fluphenazine (fluophenozine),

perphenazine, levomepromazine, thioridazine, perazine, chlorpromazine, chlorprothixine (chlorprotheaxine), zuclopentixol (*zuclopantexol*), flupentixol (*flupentexol*), prothipendyl (prithipendyl), zotepine, benperidol (penperidol), pipamperone (*piparmerone*), melperone (melperol) and bromperidol.

The form of administration according to the invention furthermore preferably does not contain any emetics. Emetics are known to the person skilled in the art and can be present as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically compatible compounds, in particular in the form of the salts or solvates thereof. Preferably, the form of administration according to the invention does not contain any emetics based on one or more ingredients of ipecacuanhae root (ipecac), eg based on the ingredient emetine, such as are described, for example, in "Pharmazeutische Biologie – Drogen und ihre Inhaltsstoffe" by Prof Dr Hildebert Wagner, 2nd, revised edition, Gustav Fischer Verlag, Stuttgart, New York 1982. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure. Preferably, the form of administration according to the invention also does not contain any apomorphine as an emetic.

Finally, the form of administration according to the invention preferably also does not contain any bitter substances. Bitter substances and the quantities effective for use may be found in US- 2003/0064099 A1, the corresponding disclosure of which should be deemed to be a disclosure of the present invention and is hereby introduced as a reference. Examples of bitter substances include aromatic oils, such as peppermint oil, eucalyptus oil, bitter almond oil, menthol, fruit aroma substances, aromatic substances from lemons, oranges, limes, grapefruit or mixtures thereof, and/or denatonium benzoate.

Therefore, the form of administration according to the invention preferably does not contain any substances with a psychotropic action, nor substances that irritate the nasal passages and/or pharynx, nor antagonists for the physiologically active substance (A), nor emetic nor bitter substances.

In a preferred embodiment the form of administration according to the invention contains as the physiologically active substance (A) a nutritional supplement. Nutritional supplements preferably contain one or more nutrients in a concentrated, measured form that is atypical of

foodstuffs. They are intended to supplement the daily diet in cases in which the diet is insufficient or a supplementation is desired. Preferably, the nutritional supplement is selected from the group consisting of vitamins, mineral supplements, trace elements, enzymes, fatty acids, amino acids, and antioxidants. Particularly preferred nutritional supplements are vitamins, provitamins and the derivatives thereof, in particular retinol, calcitriol, tocopherol, phylloquinone, thiamine, riboflavine, folic acid, niacin (in particular nicotinamide), pantothenic acid, pyridoxal, cobalamin, L-ascorbic acid, biocytin, biotin and carotenoids.

In a preferred embodiment, the form of administration according to the invention contains as the physiologically active substance (A) a therapeutic agent (= active pharmaceutical ingredient) justifying the use of the form of administration as medicinal product and being responsible for the efficacy thereof. Suitable therapeutic agents in the form of administration according to the invention are in principle all known therapeutic agents, wherein the therapeutic agents as such can be present in the form of administration according to the invention in the form of the derivatives thereof, in particular esters or ethers, or in each case in the form of corresponding physiologically compatible compounds, in particular in the form of the corresponding salts or solvates thereof, as racemates or in the enriched form of one or more stereoisomers (enantiomers or diastereomers).

Particularly preferably, the form of administration according to the invention contains one substance (A) or a plurality of substances (A) selected from the group consisting of

- agents for the treatment and prevention of diseases of the alimentary system and metabolism [A], in particular stomatological preparations [A01], agents for the treatment and prevention of acid-related disorders [A02], agents for the treatment and prevention of functional gastrointestinal disorders [A03], serotonin $5HT_3$ antagonists [A04AA], antihistamines preparations [A04AB], agents for bile and liver therapy [A05], laxatives [A06], intestinal anti-infectives [A07A], intestinal adsorbents [A07B], electrolytes with carbohydrates [A07C], intestinal anti-inflammatory agents [A07E], antidiarrhoeal microorganisms [A07F], digestives including enzymes [A09], drugs used in diabetes [A10], vitamins [A11], mineral supplements [A12], anabolic agents for systemic use [A14] and appetite stimulants [A15];

- agents for the treatment and prevention of diseases of the blood and the blood-forming organs [B], in particular antithrombotic agents [B01], antihaemorrhagics [B02], antianaemic agents [B03] and other haematological agents [B06],

- agents for the treatment and prevention of diseases of the cardiovascular system [C], in particular agents for cardiac therapy [C01], antihypertensives [C02], diuretics [C03], peripheral vasodilators [C04], vasoprotectives [C05], antihypotensive agents [C06A], ß-adrenoceptor antagonists [C07], calcium channel blockers [C08], agents acting on the renin-angiotensin system [C09] and lipid-lowering agents [C10]

- dermatologicals [D], in particular antifungals for systemic use [D01B], antipsoriatics for systemic use [D05B], anti-acne preparations for systemic use [D10B]

- agents for the treatment and prevention of diseases of the urogenital system and sex hormones [G], in particular gynaecological antiinfectives and antiseptics [G01], oxytocics [G02A], sympathomimetic labour suppressants [G02CA], prolactine inhibitors [G02CB], hormonal contraceptives for systemic use [G03] and urologicals [G04]

- systemic hormone preparations excluding sex hormones and insulins [H], in particular pituitary and hypothalamic hormones and analogues [H01], corticosteroids for systemic use [H02], thyroid preparations [H03], pancreatic hormones [H04] and agents for the regulation of the calcium homeostasis [H05],

- antiinfectives for systemic use [J], in particular antibiotics for systemic use [J01], antimycotics for systemic use [J02], antimycobacterials [J04], antivirals for systemic use [J05], immune sera and immunglobulins [J06] and vaccines [J07],

- antineoplastic and immunmodulating agents [L], in particular antineoplastic agents [L01], agents for endocrine therapy [L02], immunostimulants [L03] and immunosuppressive agents [L04];

- agents for the treatment and prevention of diseases of the musculo-skeletal system [M], in particular anti-inflammatory and antirheumatic products [M01], peripherally acting muscle

relaxants [M03A], directly acting muscle relaxants [M03C], antigout preparations [M04] and agents for the treatment of bone diseases [M05];

- agents for the treatment and prevention of diseases of the nervous system [N], in particular salicylic acid and derivatives thereof [N02BA], pyrazolones [N02BB], anilides [N02BE], ergot alkaloids [N02CA], corticosteroids derivates [N02CB], selective serotonin $5HT_1$ agonists [N02CC], hydantoin derivates [N03AB], oxazolidine derivates [N03AC], succinimide derivates [N03AD], carboxamide derivatives [N03AF], fatty acid derivatives [N03AG], antiparkinson drugs [N04]), antipsychotics [N05A], antidepressants [N06A], anti-dementia drugs [N06D], parasympathomimetics [N07A] and antivertigo preparations [N07C],

- antiparasitic products, insecticides and repellents [P], in particular antiprotozoals [P01], antihelmintics [P02] and ectoparasiticides including scabicides, insecticides and repellents [P03],

- agents for the treatment and prevention of diseases of the respiratory system [R], in particular nasal preparations [R01], throat preparations [R02], drugs for obstructive airway diseases [R03], expectorants excluding combinations with cough suppressants [R05C] and antihistamines for systemic use [R06],

- agents for the treatment and prevention of diseases of the sensory organs [S], in particular otologicals [S02];

- general nutrients [V06] and therapeutic radiopharmaceuticals [V10],

wherein once again the references in square brackets correspond to the ATC index as used by the WHO for the classification of therapeutic agents (preferred version: January 2005 or 2006).

Preferably the form of administration according to the invention contains one substance (A) or a plurality of substances (A) selected from the group consisting of 4-aminomethylbenzoic acid, abacavir, abamectin, abciximab, abibendan, abrin, acamprosat, acarbose, acebutolol, aceclidine, aceclofenac, acediasulfone, acemetacin, acenocoumarol, acetazolamide,

acetoacetic acid, acetyldigoxin, acetylandromedol, acetylcysteine, ß-acetyldigoxin, acetylhistamine, acetylsalicylic acid, acetylthiocholine, aciclovir, acipimox, acitretin, aclarubicin, aconitine, acriflavinium chloride, acrivastine, actinoquinol, acylaminopenicillin, adalimumab, adapalene, adefovir, adefovir dipivoxil, adenosine, adenosine phosphate, adenosine triphosphate, adipiodone, adrenalin, aescin, agalsidase alfa, agalsidase beta, agaricic acid, ajmaline, alanine, albendazole, alcuronium, aldesleukin, aldosterone, alemtuzumab, alendronic acid, alfacalcidol, alfuzosin, algeldrate F, alitretinoin, alizapride, allantoin F, allopurinol, allyl isorhodanate, almasilate F, almotriptan, α-acetyldigoxin, alprenolol, alprostadil, alteplase, aluminium glycinate F, aluminium hydroxide F, aluminium phosphate F, aluminium triformate, amantadine, ambazone, ambroxol, ambutonium bromide, formic acid, amicacin, amidephrine, amidotrizoic acid, amifostine, amikacin, amiloride, aminoacetic acid, aminoglutethimide, aminophylline, aminoquinuride, amiodarone, amisulpride, amitriptyline, amitryptiline, amlodipine, amorolfine, amoxicillin, amphotericin B, ampicillin, amprenavir, amylmetacresol, amyl nitrite, anagrelide, anakinra, anastrozole, ancrod, anistreplase, antazoline, antithrombin III, apomorphine, apraclonidine, aprepitant, aprindine, aprotinin, arcitumomab, arginine, aripiprazole, arsenic trioxide, artemether, articaine, ascorbic acid, asparagine, L-asparaginase, aspartic acid, atazanavir, atenolol, atomoxetine, atorvastatin, atosiban, atovaquone, atracurium, atracurium besylate, atropine, auranofin, azapropazone, azathioprine, azelaic acid, azelastine, azidothymidine, azithromycin, azlocillin, aztreonam, N2 alanyl levoglutamide, p-aminosalicylic acid,

bacampicillin, bacitracin, baclofen, balsalazide, bambuterol, bamethan, bamipine, barbexaclone, barium sulfate F, barnidipine, basiliximab, batroxobin, becaplermin, beclomethasone, bendamustine (bedamustine), befunolol, bemiparin, benactyzine, benazepril, bencyclane, bendazac, bendroflumethiazide, benperidol (penperidol), benproperine, benserazide, benzaseride, benzathine, benzatropine, benzbromarone, benzocaine, benzoyl peroxide, benzyclane, benzydamine, benzylpenicillin, benzylphenyl glycolate, betacarotene, betahistidine, betahistine, betamethasone, betanechol, betaxolol, bethanechol chloride, betiatide, bevacizumab, bexarotene, bezafibrate, bibenzonium bromide, bicalutamide, bicisate, bifonazole, bimatoprost, biperiden, bisoprolol, bivalirudin, bleomycin, blood clotting factor VII, VIII, IX, X, XIII, bornapine, bornaprine, bortezomib, bosentan, botulinum toxin type B, brimonidine, brinzolamide, brivudin, bromhexine, bromocriptine, bromperidol, brompheniramine, brotizolam, budesonide, budipine, bufexamac, buflomedil, bumetanide,

bunazosin, buphenine, bupivacaine, bupranolol, bupropion, buserelin, buspirone, busulfan, butalamine, butanilicaine, butenafine, butethamate, butinoline, butizide, butylscopolaminium,

5-chlorcarvacrol, C1 esterase inhibitor, cabergoline, cadexomer iodine, cafedrine, calcipotriol, calcitonin, calcitriol, camylofine, candesartan cilexetil, canrenoic acid, capecitabine, capreomycin, capsaicin, captopril, carazolol, carbaldrate F, carbamazepine, carbasalate calcium, carbenoxolone, carbidopa, carbimazole, carbinoxamine, carboplatin, carglumic acid, carmustine, caroverine, carteolol, carvedilol, caspofungin, cefaclor, cefadroxil, cefalexin, cefaloridine, cefamandole, cefazolin, cefdinir, cefepime, cefetamet-pivotil, cefixime, cefodizime, cefoperazone, cefotaxime, cefotiam, cefoxitin, cefpirome, cefpodoxime, cefpodoxime-proxetil, cefprozil, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, celecoxib, celiprolol, certoparin, cetirizine, cetrimide, cetrimonium bromide, cetrorelix, cetuximab, cetylpiridinium, chenodeoxycholsäure, quinidine, quinine, quinine iron citrate F, quinine tannate F, chlorambucil, chloramphenicol, chlorbutynol, chlorhexidine, chlormidazole, chlorobutanol, chloroquine, chloroxylenol, chlorphenamine, chlorphenesin, chlorphenoxamine, chlorpromazine, chlorprothixene (chlorprotheaxine), chlortalidone, chlortetracycline, chlorzoxazone, choline, chondroitin sulfate, choriogonadotropin alfa, chorionic gonadotropin, chrysarobin, chymotrypsin, ciclesonide, cicletanine, ciclopirox, ciclosporin, cidofovir, cilastatin, cilazapril, cimetidine, cinacalcet, cinchocaine, cinnarizine, cinolazepam, ciprofloxacin, cisapride, cisatracurium besylate, cisplatin, citalopram, citicoline, cladribine, clarithromycin, clavulanic acid, clemastine, clenbuterol, clindamycin, clioquinol, clobetasol, clobetasone, clobutinol, clocortolone, clodronic acid, clofibrate, clomifene, clomipramine, clonazepam, clonidine, clopamide, clopidogrel, clostebol acetate, clostridium botulinum, clotrimazole, cloxiquine, clozapine, cocarboxylase, colchicine, colecalciferol, colesevelam, colestipol, colestyramine, colfosceril palmitate, colistin, zinc eyewash F, corticorelin, corticotrophin, cortisone, cresol, croconazole, cromoglicic acid, crotamiton, cryofluorane, cumarin, cyanamide, cyanocobalamin, cyclizine, cyclobutyrol, cyclopentolate, cyclophosphamide, cycloserine, cyproheptadine, cyproterone, cysteine, cytarabin, cytarabine,

2,4-dichlorobenzyl alcohol, 2-diethylaminoethanol, dacarbazine, daclizumab, dactinomycin, dalfopristin, dalteparin, danaparoid, danazol, dantrolene, dapiprazole, dapsone, darbepoetin alfa, darifenacin, daunorubicin, deamol, deanol (deanolace), decarbazine, dectaflur F, deferiprone, deferoxamine, delapril, demeclocycline, denaverine, depreotide, dequalinium, desflurane, desipramine, desirudin, deslanoside, desloratadine, desmeninol, desmopressin,

desogestrel, desoximetasone, desoxyribonuclease, detajmium, dexamethasone, dexchlorpheniramine, dexibuprofen, dexketoprofen, dexrazoxane, dextran, dextromethorphan, diacerein, diacetyl morphine, dibenzepin, dibotermin alfa, diclofenac, diclofenamide, didanosine, dienestrol, dienogest, diethylstilbestrol, difloxacin, diflucortolone, diflunisal, digitoxin, digoxin, dihydralazine, dihydroergocornine, dihydroergocristine, dihydroergocryptine, dihydroergotamine, dihydroergotoxine, dihydrotachysterol, diisopropylamine, dikalium clorazepate, diltiazem, dimenhydrinate, dimepranol, dimercaprol, dimethyl sulfoxide, dimethindene, dinatriumselenit, dinoprost, dinoproston, diosmin, diphenhydramine, diphenoxylate, diphenylpyraline, dipivefrine, diprophylline, dipyridamole, disopyramide, dinitrogen monoxide, distigmine, disulfiram, dithranol, dixyrazine, D-norpseudoephedrine, dobesilate calcium, dobutamine, docetaxel, dofetilide, dolasetron, domperidone, donepezil, dopamine, dopexamine, dornase alfa, dorzolamide, dosulepin, doxapram, doxazosin, doxepin, doxorubicin, doxycycline, doxylamine, drofenine, droperidol, drospirenone, drotrecogin alfa, duloxetine, dutasteride, dydrogesterone, N,N'-dihydroxymethyl urea,

ebastine, econazole, ecothiopate iodide, efalizumab, efavirenz, eflornithine, iron (III) ammonium citrate F, superparamagnetic iron oxide, elcatonin, eletriptan, emedastine, emepronium, emepronium carrageenate, emetine, emtricitabine, enalapril, enalaprilat, enflurane, enfuvirtide, enoxacin, enoxaparin, entacapone, ephedrine, ephedrine racephedrine, epinastine, epinephrine, epirubicin, eplerenone, epoetin alfa, epoetin beta, epoetin delta, epoprostenol, eprazinone, eprosartan, eptacog alfa, eptifibatide, eptotermin alfa, erdosteine, ergocalciferol, ergometrine, ergotamide, ertapenem, erythromycin, escitalopram, esmolol, esomeprazole, estradiol, estramustine, estriol, estrone, etacrynic acid, etamivan, etanercept, ethacridine, ethambutol, ethaverine, ethinylestradiol, ethisterone, ethosuximide, etidronic acid, etilefrine, etodolac, etofenamate, etofibrate, etofylline, etomidate, etonogestrel, etoposide, etoricoxib, everolimus, exametazimus, exemestane, ezetimibe,

3-fluortyrosine, famciclovir, famotidine, felbamate, felbinac, felodipine, fenbufene, fendiline, fenofibrate, fenoterol, fenticonazole, fexofenadine, fibrinogen, fibrinolysin, filgrastim, finasteride, flavoxate, flecainide, flucloxacillin, fluconazole, fludarabine, fludeoxyglucose [^{18}F], fludrocortisone, flufenamic acid, flumazenil, flumetasone, flunarizine, flunisolide, fluocinolone acetonide, fluocinonide, fluocortolone, fluphenazine (fluophenozine), fluorescein dilaurate, fluorescein sodium, fluorometholone, fluorouracil, fluorphosphoric acid,

fluorsilane, fluoxetil, fluoxetine, flupentixol, fluphenazine, flupirtine, fluprednidene, flurbiprofen, flutamide, fluticasone, flutrimazole, fluvastatin, fluvoxamine, folinic acid, follitropin alfa, follitropin beta, folic acid, fomepizole, fomivirsen, fondaparinux, formestane, formoterol, fosamprenavir, foscarnet, fosfestrol, fosfomycin, fosinopril, fosphenytoin, fotemustine, framycetin, framycetin, frovatriptan, fulvestrant, furosemide, fusafungine, fusidic acid, fytic acid,

gabapentin, gadobenic acid, gadobutrol, gadodiamide, gadopentetic acid, gadoteridol, gadoteric acid, gadoteric acid -meglumine, gadoxetic acid, galantamine, gallopamil, ganciclovir, ganirelix, gatifloxacin, gemcitabine, gemfibrozil, gentamicin, gepefrine, gestodene, glatiramer, glibenclamide, glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepide, glucagon, glutamine, glutamic acid, glycopyrronium, glycopyrronium bromide, glycyrrhetinic acid, gonadorelin, goserelin, gramicidin, granisetron, grepafloxacin, griseofulvin, g-strophanthin, guajacol, guanethidine, guanfacine,

^{13}C urea, 4-hydroxybutyric acid, halcinonide, halofantrine, halometasone, haloperidol, halothane, haem, haematoporphyrin, heparin, hepatitis B vaccine, heptaminol, hexobarbital, hexobendine, hexoprenaline, histamine, histidine, homatropine, homofenazine, human albumin, hyaluronidase, hydralazine, hydrastinine, hydroquinone, hydrochlorothiazide, hydrocortisone, hydrotalcite F, hydroxocobalamin, hydroxycarbamide, hydroxychloroquine, hydroxycine, hydroxylamine, hydroxyprogesterone, hydroxyzine, hymecromone,

ibandronic acid, ibopamine, ibritumomab tiuxetan, ibuprofen, ibutilide, idarubicin, ifosfamide, iloprost, imatinib, imatinib mesylate, imidapril, imiglucerase, imipenem, imipramine, imiquimod, immunocyanin, indanazoline, indapamide, indinavir, indium chloride [^{111}In], indobufen, indometacin, indoramin, infliximab, inosine, insulin, insulin aspart, insulin detemir, insulin glargine, insulin glulisine, insulin lispro, interferon alfa, interferon alfa-2b, interferon alfacon-1, interferon beta, interferon beta-1a, interferon beta-1b, interferon gamma, iobitridol, iodine, iodamide, iodixanol, ioflupane [^{123}I], iohexol, iomeprol, iopamidol, iopentol, iopromide, iosarcol, iotrolan, iotroxic acid, ioversol, ioxaglic acid, ioxitalamic acid, ipatropium, irbesartan, irinotecan, irinotecan, isepamicin, isoaminile, isoconazole, isoflurane, isoleucine, isoniazid, isonicotinic acid, isoprenaline, isosorbide, isospaglumic acid, isotretinoin, isoxsuprine, isradipine, itraconazole,

josamycin,

potassium permanganate, kallidinogenase, kanamycin, kawain, kebuzone, ketamine, ketoconazole, ketoprofen, ketorolac, ketotifen, collagenase, creosote,

labetalol, lacidipine, lactitol, lamivudine, lamotrigine, lanreotide, lansoprazole, laronidase, latanoprost, leflunomide, lenograstim, lepirudin, lercanidipine, letrozole, leucine, leuprorelin, levallorphan, levamisole, levetiracetam, levobunolol, levobupivacaine, levocabastine, levocetirizine, levodopa, levofloxacin, levofolinate calcium, levomepromazine, levomethadyl, levonorgestrel, levopropylhexedrine, levosimendan, levothyroxine, lidocaine, lincomycin, lindane, linezolid, liothyronine, lisinopril, lisuride, lobeline, lodoxamide, lofepramine, lomefloxacin, lomustine, lonazolac, loperamide, lopinavir, loratadine, lorazepam oxide, lornoxicam, losartan, loteprednole, lovastatin, lumefantrine, lutropin alfa, lymecycline, lynestrenol, lypressin, lysine,

magaldrat F, magnesium pidolate, magnesium-L-aspartate, mangafodipir, manidipine, maprotiline, mebendazole, mebeverine, meclofenoxate, mecloxamine, meclozine, medrogestone, medroxyprogesterone, mefenaminic acid, mefloquine, megestrol, melagatrane, melitracen, melperone (melperol), melphalan, memantine, menadione, mepacrine, mepartricin, mephenytoin, mepindolol, mepivacaine, mepyramine, mequinol, mercaptamine, mercaptopurine, meropenem, mesalazine, mesna, mesterolone, mesuximide, metaclazepam, metamizole, metamphetamine, metenolone, metenolone acetate, metformin, methanthelinium, methazolamide, methenamine, methionine, methohexital, methotrexate, 5-methoxypsoralen, 8-methoxypsoralen, methyl 5-aminolevulinate, methylbenactyzium bromide, methyldopa, methylergometrine, methylprednisolone, methylrosanilinium, methyltestosterone, methylthionium chloride, methysergide, metildigoxin, metipranolol, metoclopramide, metoprolol, methixene (metrixene), metronidazole, mexiletine, mezlocillin, mianserine, miconazole, midodrine, mifepristone, miglitol, miglustat, milnacipran, milrinone, miltefosine, minocycline, minoxidil, mirtazapine, misoprostol, mitobronitol, mitomycin, mitotane, mitoxantrone, mivacurium chloride, mivacuronium, mizolastine, moclobemide, moexipril, molgramostim, molsidomine, mometasone, monochloroacetic acid, montelukast, moroctocog alfa, moxaverine, moxifloxacin, moxonidine, mupirocin, mycophenolate mofetil,

nadifloxacin, nadrolon decanonate, nadroparin calcium, naftidrofuryl, naftifine, nalbuphine, nalide, nalmefene, nalmexone, naloxone, naltrexone, naluphine, naphazoline, 2-naphthol, naproxen, naratriptan, naratriptan, nateglinide, sodim aurothiomalate, sodium phenylbutyrate, sodium fluoride, sodium hyaluronate, sodium iodide [^{131}I], sodium molybdate [^{99}Mo], sodium phenylbutyrate, n-butyl-p-aminobenzoate, n-butylscopolaminium bromide, nebivolol, nedocromil, nefazodone, nefopam, nelfinavir, neomycin, neostigmine, neostigmine methylsulfate, netilmicin, nevirapine, n-heptyl-2-phenyl glycinate, nicardipine, nicergoline, nicethamide, niclosamine, nicoboxil, nicorandil, nicotine, nicotine aldehyde, nicotinamide, nicotin resinate, nicotinic acid, nicotinic acid ester, nicotinyl alcohol, nifedipine, niflumic acid, nifuratel, nilvadipine, nimesulide, nimodipine, nimorazole, nimustine (nimustatine), nisoldipine, nitisinone, nitrendipine, nitric oxide, nitrofurantoin, nitroglycerine, nizatidine, N-methylephedrine, nonacog alfa, nonivamide, noradrenalin, norelgestromin, norepinephrine, norethisterone, norfenefrine, norfloxacin, norgestimate, norgestrel, nortriptyline, noscapine, nystatin,

obidoxime chloride, octafluoropropane, octocog alfa, octodrine, octreotide, odansetron, ofloxacin, olaflur F, olanzapine, olmesartan medoxomil, olopatadine, olsalazine, omeprazole, omoconazole, ondansetron, opipramol, oral cholera vaccine, orciprenaline, orlistat, ornipressin, orphenadrine, oseltamivir, osteogenic protein-1 (BMP-7), oxaprozin, oxatomide, oxcarbazepine, oxedrine tartrate, oxetacaine, oxiconazole, oxilofrine, oxitropium, 2-oxo-3-methylbutytric acid, 2-oxo-3-methylvaleric acid, 2-oxo-3-phenylpropionic acid, 2-oxo-4-methylvaleric acid, oxprenolol, oxybuprocaine, oxybuprocaine, oxybutynin, oxybutynin, oxyfedrine, oxymetazoline, oxytetracycline, oxytocin,

paclitaxel, palinavir, palivizumab, palonosetrone, pamidronic acid, pancuronium (pancurmium), pantoprazole, papaverine, paracetamol, paraldehyde, parecoxib, paricalcitol, parnaparin, paromomycin, paroxetine, pefloxacin, pegfilgrastim, peginterferon alfa, pegvisomant, pemetrexed, penbutolol, penciclovir, penfluridol, penicillamine, pentaerithrityl tetranitrate, pentamidine, pentetrazol, pentetreotide, pentosan polysulfate sodium, pentoxifylline, pentoxyverine, perazine, perchloric acid, perflenapent, perflisopent, perflutren, pergolide, perindopril, perphenazine, phenacetin, phenamazid, phenazone, phenazopyridine, pheniramine, phenol, phenolphthalein, phenoxybenzamine, phenoxymethylpenicillin, phenprocoumon, phentolamine, phenylalanine, phenylbutazone, phenylephrine, phenylpropanolamine, phenyltoloxamine, phenytoin, phloroglucinol, pholedrine,

phthalylsulfathiazole, physostigmine, phytomenadione, phytosterin, picric acid, pilocarpine, pimecrolimus, pimozide, pinaverium bromide, pindolol, pioglitazone, pipamperone, pipazetate, pipecuronium bromide, pipemidic acid, pipenzolate, piperacillin, piprinhydrinate, piracetam, pirarubicin, pirbuterol, pirenzepine, piritramide, piroxicam, pivmecillinam, pizotifen, podophyllotoxin, polidocanol, polycarbophil, polyestradiol phosphate, polymyxin B, polymyxin-B, polystyrenesulfonic acid, porfimer, prajmaline, prajmalium bitartrate, pramipexole, pranoprofen, prasterone, pravastatin, prazepam, prazosin, prednicarbate, prednisolone, prednisone, pregabalin, proglumetacin (preglumetacin), pridinol, prilocaine, primaquine, primidone, procaine, procainamide, procarbazil, procarbazine, procyclidin, progesterone, proglumetacin, proglumide, proguanil, proline, promethazine, propacetamol, propafenon, propanolol, propicillin, propiverine, propofol, propranolol, propylthiouracil, propyphenazone, protamine, protamine sulfate, protein C, prothipendyl (prithipendyl), prothrombin, protionamide, protirelin, proxymetacaine, proxyphylline, pseudoephedrine, pulmonal, pyrantel, pyrazinamide, pyridostigmine, pyridostigmine bromide, pyridoxine, 3-pyridylmethanol, pyrimethamine, pyrithione zinc, pyritinol, pyrogallol, pyrvinium, pyrvinium embonate,

mercury amide chloride, quetiapine, quinagolide, quinapril, quinupristin,

rabeprazole, racecadotrile, racephedrine, raloxifene, raltitrexed, ramipril, ranitidine, rasagiline, rasburicase, raubasine, reboxetine, repaglinide, reproterol, reserpine, resorcinol, reteplase, retinol, reviparin, ribavirin, riboflavin, rifabutin, rifampicin, rifamycin, rifaximin, rilmenidine, riluzol, rimexolone, risedronic acid, risperidone, ritonavir, rituximab, rivastigmine, rizatriptan, rocuronium bromide, rofecoxib, ropinirole, ropivacaine, ropivacaine, rosiglitazone, red mercuric sulfide F, roxatidine, roxithromycin,

salbutamol, salicylic acid, salmeterol, nitric acid, nitrous acid, salverine, samarium [^{153}Sm] lexidronam, saquinavir, sulfur hexafluoride, scopolamine, selegiline, selenium sulfide, serine, sermorelin, sertaconazole, sertindole, sertraline, sevelamer, sevoflurane, sibutramine, silver chloride F, sildenafil, silibinin, simvastatin, sirolimus, solifenacin, formaldehyde solution, somatostatin, somatropin, sotalol, spaglumic acid, sparteine, spectinomycin, spiramycin, spirapril, spironolactone, stavudine, streptodornase, streptokinase, streptomycin, strontium ranelate, strontium chloride, strychnine, sucralfate F, sulbactam, sulesomab, sulfacetamide, sulfadiazine, sulfadimethoxine, sulfaguanidin, sulfamerazine, sulfamethoxazole,

sulfamethoxydiazine, sulfametrole, sulfanilamide, sulfasalazine, sulfathiazole, sulfisomidine, sulindac, sulodexide, sulfur hexafluoride, sulpiride, sulprostone, sultamicillin, sultiame, sumatriptan, suxamethonium,

tacalcitol, tacrolimus, tadalafil, tamoxifen, tamsulosin, tasonermin, taurolidine, tazarotene, tazobactam, tegafur, teicoplanin, telithromycin, telmisartan, temoporfin, temozolomide, tenecteplase, teniposide, tenofovir, tenofovir disoproxil, tenoxicam, terazosin, terbinafine, terbutaline, terfenadine, teriparatide, terizidone, terlipressin, testosterone, testosterone propionate, testosterone undecanonate, tetracaine, tetracosactide, tetracycline, tetrafluoroborat-1+, tetrofosmin, tetryzoline, thallium chloride [^{201}Tl], theobromine, theodrenaline, theodrenaline, theophylline, thiamazole, thiamine, thiethylperazine, thiocolchicoside, thiopental, thioridazine, thiotepa, threonine, thrombin, thrombokinase, thymol, thyrotropin alfa, tiagabine, tianeptine, tiapride, tibolone, ticlopidine, tiludronic acid, timolol, tinzaparin, tioconazole, tioguanine, tiotropium bromide, tirilazad, tirofiban, tisopurine, tizamidine, tizanidine, tobramycin, tocainide, tolazoline, tolbutamide, tolcapone, tolfenaminic acid, tolmetin, tolperisone, tolterodine, topiramate, topotecan, torasemide, toremifene, tramazoline, trandolapril, tranexamic acid, tranylcypromine, trapidil, trastuzumab, travoprost, trazodone, tretinoin, triamcinolone, triamcinolone acetonide, triamterene, trichloroacetic acid, triethylperazine, trifluoperazine, triflupromazine, trihexyphenidyl, trimebutine, trimecaine, trimegestone, trimetazidine, trimethoprim, trimipramine, tripelenamine, triprolidine, triptorelin, tritoqualine, trofosfamide, tromantadine, trometamol, tropicamide, tropisetron, trospium, tryptophan, tubocurarine chloride, tulobuterol, tyloxapol, tyrosine, tyrothricin,

unoprostone, urapid, urapidil, urokinase, ursodeoxycholic acid,

valaciclovir, valdecoxib, valganciclovir, valinr, valproic acid, valsartan, vancomycin, vardenafil, vecuronium (vecurmium), vecuronium bromide, venlafaxin, verapamil, verteporfin, vigabatrin, viloxacine, vinblastine, vincamine, vincristine, vindesine, vinorelbine, vinpocetine, viquidil, voriconazole, votumumab,

hydrogen peroxide,

xantinol nicotinate, ximelagatrane, xipamide, xylometazoline,

yohimbine, yttrium^{90}Y chloride,

zalcitabine, zaleplon, zanamivir, zidovudine, zinc acetate dihydrate, zinc chloride, zinc citrate, zinc sulfate, ziprasidone, zofenopril, zoledronic acid, zolmitriptan, zolpidem, zolpidem tartrate, zonisamide, zopiclone, zotepine and zuclopenthixol (zucklopantexol).

The aforementioned compounds are primarily referred to by their International Nonproprietary Names (INN) known to the person skilled in the art. Further details may be found, for example, in International Nonproprietary Names (INN) for Pharmaceutical Substances, World Health Organisation (WHO).

In a preferred embodiment, the form of administration according to the invention contains one substance (A) or a plurality of substances (A) selected from the group consisting of 1,1-(3-dimethylamino-3-phenylpentamethylen)-6-fluor-1,3,4,9-tetrahydropyrano[3,4-b]indole, in particular its hemicitrate, 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylen]-1,3,4,9-tetrahydropyrano[3,4-b]indole, in particular its citrate and 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylen]-1,3,4,9-tetrahydropyrano[3,4-b]-6-fluoro-indole, in particular its hemicitrate. The aforementioned substances are known in the prior art (see WO 2004/043967, WO 2005/066183).

Furthermore, in addition to the achievement of the necessary resistance to breaking of the form of administration according to the invention, at least one natural, semi-synthetic or synthetic wax (D) can be used (= component (D)). Preferably, waxes with a softening point of at least 50°C, more preferably at least 55°C, still more preferably at least 60°C, most preferably at least 65°C and in particular at least 70°C. Particularly preferable are carnauba wax and beeswax. Quite particularly preferable is carnauba wax. Carnauba wax is a natural wax obtained from the leaves of the carnauba palm and has a softening point of at least 80°C. With the additional use of the wax component, it is used together with at least one polymer (C) in such quantities that the form of administration has a resistance to breaking of at least 400 N, preferably at least 500 N.

Suitable for use as excipients (B) are the usual known excipients for the formulation of solid forms of administration. Preferably, these are plasticisers, such as triacetin and polyethylene

glycol, preferably a low-molecular polyethylene glycol, excipients, influencing the release of the active ingredient, preferably hydrophobic or hydrophilic, preferably hydrophilic polymers, quite particularly preferably hydroxypropylmethylcellulose and/or antioxidants. Preferably used as hydrophilic matrix materials are polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins. Quite particularly preferable used as matrix materials are ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, poly(meth)acryl acid and/or the derivatives thereof, such as the salts, amides or esters thereof.

Suitable antioxidants are ascorbic acid, butylhydroxyanisole (BHA), butylhydroxytoluene (BHT), salts of ascorbic acid, monothioglycerol, phosphorous acid, vitamin C, vitamin E and the derivatives thereof, sodium bisulfite, particularly preferably butylhydroxytoluene or butylhydroxyanisole and α-tocopherol.

The antioxidant is preferably in quantities of 0.01 to 10 % by weight, preferably 0.03 to 5 % by weight, based on the total weight of the form of administration.

The forms of administration according to the invention are characterised by the fact that due to their resistance to breaking, they cannot be pulverised by means of the usual comminution means, such as a mortar and pestle. This means an overdose is virtually impossible. However, in order further to increase the resistance to breaking of the form of administration, the forms of administration according to the invention can contain further means for enhancing resistance to breaking as excipients (B).

The form of administration according to the invention is preferably solid and is suitable for oral, vaginal or rectal, preferably oral administration. It is preferably not in film form. In a further preferred embodiment, the form of administration according to the invention is present in the form of a tablet, a capsule or in the form of an oral osmotic therapeutic system (OROS).

In a preferred embodiment, the form of administration according to the invention is present as a tablet.

The form of administration according to the invention can be present in multiparticulate form, preferably in the form of microtablets, microcapsules, micropellets, granules, spheroids, beads

or pellets, optionally packaged into capsules or press into tablets, preferably for oral administration. Hereby, preferably the individual particles as such have a resistance to breaking of at least 400 N, optionally also a tablet produced therefrom.

Preferably, the multiparticulate forms have a size or size distribution in the region of 0.1 to 3 mm, in particular preferably in the region of 0.5 to 2 mm. Depending upon the desired form of administration, the usual excipients (B) are optionally also used for the formulation of the form of administration.

The form of administration according to the invention can be produced by different methods, which are explained in greater detail below; the invention also relates to forms of administration obtainable by any of these methods:

The method to produce of the form of administration according to the invention preferably comprises the following steps:

(a) mixing of component (A), optionally (B), (C), optionally (D),

(b) optionally preforming the mixture obtained from step (a) mixture, preferably by applying heat and/or force to the mixture obtained from (a), wherein the quantity of heat supplied is preferably not sufficient to heat component (C) to its softening point,

(c) hardening of the mixture by applying heat and force, wherein the supply of heat can take place during and/or before the application of force and quantity of heat supplied is sufficient to heat the component (C) at least to its softening point,

(d) optionally singulating the hardened mixture,

(e) optionally shaping the form of administration and

(f) optionally coating with a film coating.

The heat can be supplied directly or by means of ultrasound. The application of force and/or the shaping of the form of administration can take place, for example, by direct tabletting or

by means of suitable extruders, in particular with twin-screw extruders (roller die extruders) or planetary gear extruders.

The following method variants are particularly preferable:

Method variant 1:

In this embodiment, the form of administration according to the invention is preferably produced without the use of an extruder, wherein preferably components (A), optionally (B), (C) and the optionally present component (D) are mixed and the resulting mixture, optionally after granulation, is shaped into the form of administration with the preceding or simultaneous application of heat.

This heating and application of force to produce the form of administration is performed without the use of an extruder.

The mixing of the components (A), optionally (B), (C) and optionally (D) is performed in a mixer known to the person skilled in the art. The mixer can be for example a roll mixer, shaking mixer, shear mixer or compulsory mixer.

The resultant mixture is preferably shaped directly into the form of administration according to the invention by the application of force with the preceding or simultaneous application of heat. For example, the mixture can be shaped into tablets by direct tabletting. With direct tabletting with the simultaneous application of heat, the tabletting tool, ie the lower punch, upper punch and the die, is used to heat mixture to be pressed to at least the softening point of the polymer component (C) and then pressed. With direct tabletting with the preceding application of heat, the material to be pressed is heated immediately prior to tabletting to at least the softening point of the component (C) and then pressed by means of the tabletting tool.

So, for example, a tabletting tool with upper punch, lower punch and die for tablets with a 10 mm diameter and a radius of curvature of 8 mm can be used to press 300 mg of powder mixture at a temperature of 80°C, wherein the pressure resulting from application of a force of for example 2 kN or 4 kN can be maintained for 15 s, for example.

The resultant mixture of the components (A), optionally (B), (C) and optionally component (D) can also be first granulated and then be shaped into the form of administration according to the invention under the application of force with the preceding or simultaneous application of heat.

Each time force is applied, this is continued until the form of administration has achieved a breaking resistance of at least 400 N, 420 N, 440 N, 460 N, 480 N, preferably at least 500 N.

The granulation can be performed in known granulators by moist granulation or melt granulation.

Each of the known method steps, in particular the heating and simultaneous or subsequent application of force to produce of the form of administration according to the invention is performed without the use of an extruder.

Method variant 2:

In this method variant, the form of administration according to the invention is produced by thermoforming by means of an extruder without thereby any discoloration of the extrudate being observed.

To investigate the degree of discoloration caused by this thermoforming, the colour of the mixture of the starting components of which the form of administration consists is first determined without the addition of a colour-imparting component, such as, for example, a coloured pigment or a coloured component (eg α-tocopherol). This composition is then thermoformed according to the invention, wherein all method steps including the cooling of the extrudate are performed under an inert gas atmosphere. By way of comparison to this, the same composition is produced using the same method but without an inert gas atmosphere. The coloration is determined of the form of administration produced according to the invention from the starting composition and the form of administration produced for purposes of comparison. The determination is performed with the assistance of "Munsell Book of Colour" from Munsell Colour Company Baltimore, Maryland, USA, 1966 edition. If the coloration of the form of administration thermoformed according to the invention has a

coloration with the identification No N 9.5/ but at the most a coloration with the identification No 5Y 9/1, the thermoforming is classed as being "without discoloration". If the form of administration has a coloration with the identification No 5Y 9/2 or more, determined in accordance with the Munsell Book of Colour, the thermoforming is classed as being "with discoloration".

Surprisingly, the forms of administration according to the invention exhibit no discoloration that can be classified in accordance with the above classification if the entire production method is performed under an inert gas atmosphere, preferably under a nitrogen atmosphere by means of an extruder for thermoforming.

This variant according to the invention for the production of the forms of administration according to the invention is characterised by the fact that

z) components (A), optionally (B), (C) and the optionally present component (D) are mixed,

y) the resultant mixture is heated in the extruder to at least the softening point of component (C) and extruded by the application of force through the outlet orifice of the extruder,

x) the still plastic extrudate is singulated and shaped into the form of administration or

w) the cooled and optionally reheated singulated extrudate is shaped into the form of administration,

wherein the method steps y) and x) and optionally the method steps z) and w) are performed under an inert gas atmosphere, preferably a nitrogen atmosphere.

The mixing of the components according to method step z) can also take place in the extruder.

The mixture of components (A), optionally (B), (C) and optionally (D) can also be performed in a mixer known to the person skilled in the art. The mixer can be for example a roll mixer, shaking mixer, shear mixer or compulsory mixer.

Before mixing with the further components, component (C) and the optionally present component (D) according to the invention is preferably provided with an antioxidant. This can take place by mixing the two components (C) with the antioxidant, preferably by dissolving or suspending the antioxidant in a highly volatile solvent and homogeneously mixing this solution or suspension with component (C) and the optionally present component (D) and removing the solvent by drying, preferably under an inert gas atmosphere.

The, preferably molten, mixture which has been heated in the extruder to at least the softening point of component (C) is extruded from the extruder through a die with at least one bore.

The performance of the method process according to the invention requires the use of suitable extruders, preferably screw extruders (roller die extruders), wherein extruders which are equipped with two screws (rollers) are particularly preferred.

The extrusion is preferably performed so that the expansion of the extruded strand is preferably at the most 50%, ie, that when using an extrusion die with a diameter of 6 mm for example, the extruded strand should have a diameter of at the most 9 mm. More preferably, the expansion of the strand is at the most 40%, still more preferably at the most 35%, most preferably at the most 30% and in particular at the most 25%. It has surprisingly been found that if the extruded material in the extruder is exposed to a severe mechanical stress, a significant expansion of the strand occurs thereby resulting in undesirable irregularities of the properties, in particular the mechanical properties, of the extruded strand.

Preferably, the extruder comprises at least two temperature zones, wherein in the first zone, which is downstream from a feed zone and optionally a mixing zone, the heating of the mixture takes place up to at least the softening point of component (C). The throughput of the mixture is preferably from 2.0 kg to 8.0 kg/hour.

After heating to at least the softening point of component (C), the molten mixture is conveyed by means of screws, further homogenised, compressed or compacted, so that, immediately before emerging from the extruder die, it has a minimum pressure of 5 bar, preferably of at least 10 bar, and is extruded through the die as an extruded strand or extruded strands, depending on the number of bores which the die comprises. The die geometry or the geometry of the bores is freely selectable. For example, the die or the bores can have a round, oblong or

oval cross section, wherein the round cross section preferably has a diameter of 0.1 mm to 15 mm and the oblong cross section preferably has a maximum lengthwise extension of 21 mm and a crosswise extension of 10 mm. Preferably, the die or the bores have a round cross section. The casing of the extruder used according to the invention can be heated or cooled. The corresponding temperature control, ie heating or cooling, is arranged so that the mixture to be extruded has at least an average temperature (product temperature) corresponding to the softening point of component (C) and does not rise above a temperature at which the physiologically active substance (A) to be processed may be damaged. Preferably, the temperature of the mixture to be extruded is adjusted to below 180°C, preferably below 150°C, but at least to the softening temperature of component (C).

After the extrusion of the molten mixture and, optionally, cooling of the extruded strand or the extruded strands, the extrudates are preferably singulated. This singulation can preferably be performed by cutting up the extrudates by means of revolving or rotating knives, water jet cutters, wires, blades or by means of laser cutters.

An inert gas atmosphere is not necessary for the intermediate or final storage of the optionally singulated extrudate or the final shape of the form of administration according to the invention.

The singulated extrudate may be pelletised with conventional methods or be pressed into tablets in order to impart the final shape to the form of administration. It is, however, also possible not to singulate the extruded strands and, and by means of contrarotating calender rolls comprising opposing recesses in their outer sleeve, to form them into the final shape, preferably a tablet, and to singulate these by conventional methods

If the optionally singulated extrudate is not immediately to be shaped into the final shape, but instead cooled for storage, after the period of storage, an inert gas atmosphere, preferably a nitrogen atmosphere, should be provided and must be maintained during heating of the stored extrudate up until plasticisation and final shaping into the form of administration.

The application of force in the extruder onto the at least plasticised mixture is adjusted by controlling the rotational speed of the conveying device in the extruder and the geometry thereof and by dimensioning the outlet orifice in such a manner that the pressure necessary for

extruding the plasticised mixture is built up in the extruder, preferably immediately prior to extrusion. The extrusion parameters necessary for each particular composition to produce a form of administration with a resistance to breaking of at least 400 N, preferably of at least 500 N, can be established by simple preliminary testing.

Suitable for extrusion is, for example, a twin-screw-extruder made by the Leistritz, (Nuremberg) of the type Micro 27 GL 40 D, screw diameter 18 mm. Screws having eccentric screw tips may be used. A round-section die with a diameter of 8 mm can be used as a die. The entire extrusion method should be performed under a N_2 atmosphere. The extrusion parameters can be adjusted, for example, to the following values: screw speed: 100 rpm, throughput: 4 kg/h; product temperature: 125°C; and casing temperature: 120°C.

Method variant 3:

With this method variant to produce the form of administration according to the invention, heat is supplied by means of ultrasound.

To this end, first of all a homogeneous mixture of at least component (A) and component (C) (= binder) is produced. Further excipients, such as for example fillers, plasticisers, lubricants or dyes, may also be incorporated into this mixture. A low molecular weight polyethylene glycol is preferably used as a plasticiser.

Mixing may be performed by means of conventional mixers. Examples of suitable mixers are roll mixers, which are also known as tumbler, drum or rotary mixers, container mixers, barrel mixers (drum hoop mixers or tumbling mixers) or shaking mixers, shear mixers, compulsory mixers, plough bar mixers, planetary kneader-mixers, Z kneaders, sigma kneaders, fluid mixers or high-intensity mixers.

The selection of the suitable mixer is determined inter alia by the free-flowing properties and cohesive strength of the material to be mixed.

The mixture is then subjected to shaping. The mixture is preferably shaped during or after the application of ultrasonication, preferably by compaction.

During the ultrasonication, it is particularly preferable that there is direct contact between the mixture and the sonotrode of the ultrasound device. An ultrasound device as shown in Figure 1 is preferably used in the method according to the invention

In this Figure 1, (1) denotes the press, with which the necessary force is applied, (2) the converter, (3) the booster, (4) the sonotrode, (5) the shaping die, (6) the lower punch, (7) the base plate, (8) and (9) the ultrasound generator and device controller. The reference numbers used relate solely to Figure 1.

During the ultrasonication, a frequency of 1 kHz to 2 MHz, preferably of 15 to 40 kHz, should be maintained. The ultrasonication should be performed until softening of the polymer (C) is achieved. This is preferably achieved within a few seconds, particularly preferably within 0.1 to 5 seconds, preferably 0.5 to 3 seconds.

The ultrasonication and the application of force ensure uniform energy transfer thus achieving the rapid and homogeneous sintering of the mixture. This produces forms of administration with a resistance to breaking of at least 400 N, preferably of at least 500 N, which hence cannot be pulverised.

Before shaping is performed, the mixture may be granulated after the mixing operation, after which the resultant granules are shaped into the form of administration, such as tablets, by ultrasonication and the application of force.
Granulation may be performed in machinery and apparatus known to the person skilled in the art.

If granulation is performed as wet granulation, water or aqueous solutions, such as for example ethanol/water or isopropanol/water, may be used as the granulation liquid.

The mixture or the granules produced therefrom may also be subjected to melt extrusion for further shaping, wherein the mixture is converted into a melt by ultrasonication and the application of force and then extruded through dies. The strands or strand obtained in this manner may be singulated to the desired length using known devices. The shaped articles singulated in this manner may optionally furthermore be converted into the final shape with ultrasonication and application of force.

The final shaping to the form of administration is preferably performed by the application of force in appropriate moulds.

The above-described formed articles may also be produced according to a calendering process by initially plasticising the mixture or the granules produced therefrom by means of ultrasonication and the application of force and extruding through a suitable die. These extrudates are then shaped into the final shape between two contrarotating shaping rolls, preferably under the application of force.

As already mentioned, shaping to produce the final shape of the form of administration by using a mixture of substance (A) and the polymer (C) with a resistance to breaking of at least 400 N, preferably of at least 500 N, is preferably performed in powder form by direct compression with the application of force, wherein ultrasonication of this mixture is provided before or during the application of force. The force is at most the force that is conventionally used for shaping forms of administration such as tablets, or for pressing granules into the corresponding final shape.

The tablets produced according to the invention may also be multilayer tablets.

In the case of multilayer tablets, at least the layer that contains substance (A) should be exposed to ultrasound and the application of force.

The corresponding necessary application of force may also be applied to the mixture by means of extruder rolls or calender rolls. Preferably, the shaping of the forms of administration is performed by the direct pressing of a powdered mixture of the components of the form of administration or corresponding granules formed therefrom, wherein ultrasonication is preferably performed during or before shaping. Such exposure is continued until the polymer (C) has softened, which is conventionally achieved in less than 1 second to at most 5 seconds.

Suitable as a press is, for example, a Branson WPS, 94-003-A, Pneumatic (Branson Ultraschall, Dietzenbach, Germany) with a plain press surface. A suitable generator (2000 W) is, for example, a Branson PG-220A, 94-001-A analogue (Branson Ultraschall) with a

sonotrode diameter of 12 mm. A die with a diameter of 12 mm can be used, whereby the bottom of the die is formed by a lower punch with a plain press-surface and a diameter of 12 mm. Suitable parameters for plastification are frequency: 20 kHz; amplitude: 50%; force: 250 N. The ultrasonication and the application force by means of the sonotrode may be maintained for 0.5 seconds, for example, wherein the ultrasonication and application of force preferably take place simultaneously.

Method variant 4:

With this method variant to produce the form of administration according to the invention, components (A), (C) and optionally (D) and optionally present excipients (B), such as antioxidants, plasticisers and/or release-delaying excipients are processed by means of a planetary-gear extruder to produce the form of administration according to the invention.

Planetary-gear extruders are known and described inter alia in detail in the Handbuch der Kunststoff-Extrusionstechnik I (1989) "Grundlagen" in Chapter 1.2 "Klassifizierung von Extrudern", pages 4 to 6. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

The following explains the use of a planetary-gear extruder in the method according to the invention with reference to Figures 2 and 3. These explanations are given merely by way of example and do not restrict the general concept of the invention

Figure 2 shows a section through a planetary gear extruder and

Figure 3 shows the mode of operation of the planetary gear extruders.

Figure 2 shows a planetary-gear extruder that may be used in the method according to the invention. This extruder substantially comprises a shaft 1, which, relative to the direction of transport of the mixture of the components listed above to be extruded, is initially constructed as a feed screw 5 and subsequently as the central spindle 3 of the planetary-gear extruder. Around the central spindle 3, there are preferably arranged three to seven planetary spindles 4, which are in turn surrounded by a casing in the form of a housing 6.

In the planetary-gear extruder, the extrusion of the composition used in the method according to the invention for the production of a form of administration preferably proceeds as follows, with reference to Figure 2. As shown by the arrow 2, the components to be extruded are apportioned by the apportioning unit 7 in the area of the feed screw 5 and conveyed by the rotation thereof (drive not shown) in the direction of the central spindle 3. The person skilled in the art will understand that it is possible to mix the starting materials (components) in the area of the feed screw. However, it is also possible to premix the components of the form of administration and to apportion this mixture via the apportioning unit 7 in the area of the feed screw 5. The mixture is conveyed into the feed zone of the planetary-gear extruder. By heating to at least the softening point of component (C), the mixture is melted and the molten mixture is conveyed into the area of the central spindle, ie the extrusion zone, by the interaction of the central spindle 3 and the planetary spindles 4, further homogenised, compressed or compacted and extruded through the die 8 as an extruded strand or extruded strands, depending on how many bores the die comprises. The die geometry or the geometry of the bores is freely selectable. Thus, the die or the bores may exhibit a round, oblong or oval cross-section, wherein the round cross-section preferably has a diameter of 0.1 mm to 15 mm and the oblong cross-section preferably has a maximum lengthwise extension of 21 mm and a crosswise extension of 10 mm. The extrusion die may also take the form of a slot die. Preferably, the die or the bores have a round, oval or oblong cross-section. Both the casing 6 of the planetary-gear extruder used according to the invention and the central spindle may be heated or cooled. The corresponding temperature control, i.e. heating or cooling, is so arranged that the mixture to be extruded exhibits an average temperature corresponding to the softening point of component (C) and does not rise above a temperature at which the substance (A) to be processed may be damaged. Preferably, the temperature of the mixture to be extruded is adjusted to below 180°C, preferably below 150°C, but at least to the softening point of component (C). The reference numbers used relate solely to Figures 2 and 3.

Following the extrusion of the molten mixture and, optionally, cooling of the extruded strand or extruded strands, the extrudates are singulated (not shown in Figure 2). This singulation can preferably be performed by cutting up the extrudates by means of revolving or rotating knives, water jet cutters, wires, blades or with the assistance of laser cutters.

Optionally after further cooling of the singulated extrudates, which are preferably present in the form of disks, they are optionally re-shaped into the final shape of the form of administration, wherein they can be exposed to heat again if necessary.

This shaping, for example into tablets, may proceed in that the plastic extrudate is shaped with press-forming with the assistance of two contrarotating rolls preferably with mutually opposing recesses for plastification in the roll sleeve, with the design of the recesses determining the tablet shape.

However, it is also possible to form the tablets from the singulated extrudates in each case with the assistance of an optionally heated die and at least one shaping punch. To this end, the cylindrical granules obtained after singulation of the extruded strand can preferably be used. Apart from being pressed into tablets, these granules or other multiparticulate shapes obtained, such as pellets or spheroids, can also be packaged into capsules in order to be used as a form of administration produced according to the invention.

In a further preferred embodiment, the extruded strands extruded through a plurality of bores in the extrusion die can, after cooling thereof, optionally be brought together by interlacing or wrapping in the manner of rope production to produce a thicker strand than the individual extruded strands. This strand can optionally be further processed by partially dissolving with a suitable solvent or by heating to the softening point of the polymer (C) and optionally removing the solvent in accordance with the above-stated singulation and shaping of an individual strand.

Figure 3 shows a cross-section through the planetary-gear extruder. Around the rotating central spindle 3 there are arranged at least three, in the case illustrated 6, planetary spindles 4, the flanks 41 of which interact on the one hand with the flank 31 of the central spindle 4 and on the other hand with the flanks 61 of the casing 6 of the planetary-gear extruder. The rotation of the central spindle 3 and the rolling of the respective flanks over one another cause the planetary spindles 4 each to rotate around their own axis, as shown by arrow 42, and around the central spindle 4, as shown by arrow 43. In this way, the compression or compaction sought according to the invention of the component mixture used according to the invention of the forms of administration produced according to the invention is achieved. The reference numbers used relate solely to Figures 2 and 3.

If necessary, the planetary-gear extruder used can comprise not only an extrusion zone but also at least one further zone, in order that the mixture to be extruded can also optionally be degassed.

The process according to the invention can be performed discontinuously or continuously, preferably continuously.

A suitable extruder is, for example, a planetary gear extruder with four planetary spindles of the type BCG 10 (LBB Bohle, Ennigerloh, Germany) with an extrusion die with a diameter of 8 mm. A gravimetrical dosing of 3.0 kg/h is suitable. The extrusion can be performed, for example, with a rotational speed of 28.6 rpm and a product temperature of about 88°C.

Method variant 5:

This variant for the production of the form of administration according to the invention is performed by processing at least the components (A), (C) and optionally (D) and optionally present excipients (B), such as antioxidants, plasticisers and/or release-delaying excipients, with the addition of a solvent for component (C), ie for the polymer or polymers (C), to produce the form of administration.

To this end, components (A), optionally (B), (C) and the optionally present component (D) are mixed and, after addition of the solvent and optionally after granulation, the resultant formulation mixture is shaped to produce the form of administration.

The mixing of components (A), optionally (B), C and optionally (D) is performed in a mixer known to the person skilled in the art. The mixer can be, for example, a roll mixer, shaking mixer, shear mixer or compulsory mixer.

The solvent for the polymer (C) is added at least in such quantities that the formulation mixture is uniformly moistened

Suitable solvents for the polymer (C) are preferably aqueous solvents, such as water, mixtures of water and aliphatic alcohols, preferably C1 to C6 alcohols, esters, ethers, hydrocarbons,

particularly preferably distilled water, short-chain alcohols, such as methanol, ethanol, isopropanol, butanol or aqueous alcohol solutions.

The solvent is preferably added under agitation. The uniformly moistened composition is then dried. Drying preferably proceeds by the application of heat at temperatures at which it is possible to rule out any discoloration of the composition. This temperature can be established by simple preliminary testing.

Before or after the drying, the composition can be divided into sub-portions that preferably in each case correspond to the mass of a unit of the form of administration. The corresponding dried portions are then shaped to produce the form of administration.

This is preferably performed by using tablet presses.

It is also possible to moisten the formulation mixture that, before addition of the solvent, the formulation mixture is divided, preferably in moulds, into sub-portions, dispersed in a liquid dispersant with stirring and then the solvent is added. Component (C) is not soluble in the dispersant, which must be miscible with the solvent.

Suitable dispersants are preferably hydrophilic solvents, such as aliphatic alcohols, ketones, esters. Short-chain alcohols are preferably used.

Alternatively, the formulation mixture can also be moistened in such a manner that the solvent is incorporated into the formulation mixture as a foam. Such a foam of the solvent is preferably produced with the means of a high-speed mixer, preferably with the addition of conventional foam stabilisers. Suitable stabilisers are, for example, hydrophilic polymers such as for example hydroxypropylmethylcellulose.

Preferably, the foam is also incorporated into the formulation mixture under agitation which preferably results in a granulated composition.

Before or after being divided into sub-portions, which preferably correspond to the mass of a unit of the form of administration, the granulated composition is dried and then shaped into the form of administration.

Drying and shaping can preferably proceed as described above. The method according to the invention can also be performed in such a manner that solvent is added to the formulation mixture in such a quantity that a shapeable paste is obtained.

Before or after being dried, which may be performed as explained above, a paste of this kind can be divided into sub-portions and the dried portions, after further division in each case into a portion corresponding to the mass of a unit of the form of administration, are shaped or converted to yield the form of administration.

It is possible int his regard to form the sub-portions in the form of strands, which may be produced by means of a screen or a strand former. The dried strands are preferably singulated and shaped to produce the form of administration. This shaping is preferably performed by means of a tablet press, using shaping rollers or shaping belts equipped with rollers.

It is also possible to convert the paste into a planar structure and to stamp the form of administration out of the dried structure.

Advantageously, the paste is processed by means of an extruder, wherein, depending on the type of the extrusion, strands or planar structures are produced, which are singulated by chopping, cutting or stamping. The singulated sub-portions may be shaped, formed or stamped as described above to produce the form of administration. Corresponding devices are known to the person skilled in the art

In this regard, the method according to the invention may here be performed continuously or discontinuously.

It is also possible to add solvent to the formulation mixture in such a quantity that at least the polymer component (C) is dissolved. A solution or dispersion/suspension of this kind is preferably converted into a planar structure, wherein preferably an extruder with a flat die is used or the solution is cast onto a planar support.

As described above, after drying, the forms of administration can be obtained from the planar structures by stamping or calendering. It is also possible, as described above, to convert the

solution into strands and to singulate these, preferably after they have been dried, and shape them to produce the form of administration.

Alternatively, the solution can also be divided into portions such that, after drying, they each correspond to the mass of a unit of the form of administration, wherein with moulds which already correspond to the shape of the unit of the form of administration are preferably used for this purpose.

If the solution is divided into any desired portions, after drying, the portions can optionally be combined again and be shaped to obtain the form of administration, such as, for example, packaged in a capsule or pressed to form a tablet.

Preferably, the formulation mixtures combined with solvent are processed at temperatures of 20°C to 40°C, wherein, apart from during drying to remove the solvent and the optionally present dispersant, no higher temperatures are used. The drying temperature must be selected below the decomposition temperature of the components. Optionally, after shaping to obtain the form of administration, further drying corresponding to the above-described drying may be performed.

Combinations of individual steps of the above method variants are also possible in order to produce the form of administration according to the invention.

The above-described method variants 2 and 4 comprise the extrusion of a composition comprising components (A), (C), optionally (B) and optionally (D). Preferably, extrusion is performed by means of twin-screw-extruders or planetary-gear-extruders, wherein twin-screw extruders are particularly preferred.

It has surprisingly been found that extrudates exhibiting an advantageous morphology are obtainable by means of planetary-gear-extruders and twin-screw-extruders. For example, it has been found that under suitable conditions the extrudate is surrounded by a shell that may be denoted as "extrusion skin". Said extrusion skin can be regarded as a sleeve-like or tubular structure forming a circumferential section of the extrudate about its longitudinal extrusion axis so that the outer surface of said sleeve-like or tubular structure forms the closed shell of

the extrudate. Usually, only the front faces of the extrudate are not covered by the extrusion skin.

The extrusion skin differs in its morphology from the core of the extrudate, which it surrounds in a sleeve-like manner and is connected thereto preferably in a seamless manner. Usually, the extrusion skin is visible with the naked eye in the cross section of the extrudate, optionally by means of a microscope, since due to the different morphology of the material forming the core and that forming the extrusion skin, their optical properties also differ. It appears that due to the extrusion process, the material forming the extrusion skin is exposed to mechanical and thermal conditions differing from the conditions to which the material forming the core of the extrudate is exposed, the consequence of which is that a heterogeneous morphology of the extruded strand is obtained, with, for example, a radial symmetry when an extrusion die with circular shape is used. Hereby, the material forming the extrusion skin and the material forming the core are usually distinguished by their morphology, preferably, however, not by their composition, in particular not by the relative content of components (A), (C), optionally (B) and optionally (D).

The extrusion skin usually covers the entire shell of the extrudate in the sense of a one-piece tubular sleeve, independently of the geometry chosen for the extrusion die. Therefore, the extrudate can have circular, elliptic or even other cross sections.

The extrusion skin preferably has a uniform thickness. Preferably, the layer thickness of the extrusion skin is within the range from 0.1 to 4.0 mm, more preferably 0.15 to 3.5 mm, still more preferably 0.2 to 3.0 mm, most preferably 0.2 to 2.5 mm and in particular 0.2 to 2.0 mm. In a preferred embodiment the sum total of the thickness of the extrusion skin over both opposing sides amounts to 0.5 to 50%, more preferably 1.0 to 40%, still more preferably 1.5 to 35%, most preferably 2.0 to 30% and in particular 2.5 to 25% of the diameter of the extrudate.

Figure 4 shows a schematic view of extrudate (71) with a sleeve-like extrusion skin (72) entirely surrounding the core (73) about the longitudinal extrusion axis (74). The outer surface of extrusion skin (72) forms the shell (75) of the extrudate (71).

It has surprisingly been found that extrudates with an extrusion skin of this kind have beneficial mechanical properties. They are particularly suitable as intermediates in the production of the forms of administration according to the invention, because they may be advantageously processed, in particular by singulating and/or shaping.

If the forms of administration according to the invention are produced by means of extrusion processes in which the above-described extrudate with an extrusion skin is obtained as an intermediate, the forms of administration obtained therefrom are preferably also characterised by a particular morphology.

In a preferred embodiment, those regions, which have formed the extrusion skin in the extruded intermediate, are still visible with the naked eye, optionally by means of a microscope, in the cross section of the form of administration. This is due to the fact that usually the further processing, in particular the singulating and/or shaping of the extrudate causes the different nature and thereby also the different optical properties of the material forming the extrusion skin and the material forming the core to be maintained. In the following, that region of the form of administration that has emerged from the extrusion skin in the course of further processing of the extrudate (intermediate) into the form of administration, will be referred to as the "sleeve-shaped region".

Preferably, the form of administration according to the invention comprises a sleeve-shaped region and a core located therein. In this regard, the sleeve-shaped region is preferably connected to the core in a seamless manner. Preferably both the sleeve-shaped region and the core have substantially the same chemical composition, ie substantially the same relative content of components (A), (C), optionally (B) and optionally (D). In this regard, the material forming the sleeve-shaped region has a morphology differing from the material forming the core. Usually, this different morphology is also expressed in terms of different optical properties, so that the sleeve-shaped region and the core are visible with the naked eye in the cross-section of the form of administration.

If the form of administration according to the invention is coated, for example with a film coating, the sleeve-shaped region is arranged between the film coating and the core.

Since the extrudate containing the extrusion skin (intermediate) can be processed in different ways to obtain the form of administration according to the invention, the sleeve-shaped domain can adopt different arrangements and extensions within the form of administration according to the invention. However, common to all arrangements is the fact that the sleeve-shaped region partially covers the surface of the core, but usually not its entire surface. Preferably, two opposite surfaces of the core are not covered, or at least not fully covered by the sleeve-shaped region. In other words, preferably the sleeve-shaped region has two openings/recesses on opposing sides.

The sleeve-shaped region can have a uniform layer thickness. It is also possible, however, that during the processing, the shaping (eg press-forming) of the extrudate can cause different regions of the extrusion skin to be compressed or extended to different degrees so that the layer thickness of the sleeve-shaped region within the form of administration can vary.

Preferably the layer thickness of the sleeve-shaped region is within the range from 0.1 to 4.0 mm, more preferably 0.15 to 3.5 mm, still more preferably 0.2 to 3.0 mm, most preferably 0.2 to 2.5 mm and in particular 0.2 to 2.0 mm

Figures 5A and 5B are two schematic views of preferred arrangements of the sleeve-shaped region within the form of administration according to the invention. In this regard, the forms of administration (81) comprise a sleeve-shaped region (82) partially surrounding the core (83). The opposing surfaces (84a) and (84b) of the core (83), however, are not covered by the sleeve-shaped region (82).

The method for the production of the form of administration according to the invention is preferably performed continuously. Preferably, the method involves the extrusion of a homogeneous mixture of components (A), (C), optionally (B) and optionally (D). In this regard, it is particularly advantageous for the intermediate obtained, eg the strand obtained by extrusion, to have uniform properties. Particularly desirable are uniform density, uniform distribution of the active substance, uniform mechanical properties, uniform porosity, uniform surface finish, etc. Only under these circumstances can the uniformity of the pharmacological properties, such as the stability of the release profile, be ensured and the amount of rejects kept low.

Preferably, the method according to the present invention may be performed in such a way that the quantity of rejects is less than 25%, more preferably less than 20%, most preferably less than 15% and in particular less than 10%, wherein the rejection criteria are the FDA standards regarding the intervariability of the content of component (A), its release profile and/or the density of the form of administration when comparing two forms of administration, preferably taken from the same batch.

It has surprisingly been found that the above properties may be obtained by means of twin-screw-extruders and planetary-gear-extruders, wherein twin-screw-extruders are particularly preferred.

The method according to the invention preferably involves the extrusion of a mixture of components (A), (C), optionally (B) and optionally (D), preferably by means of a planetary-gear-extruder or a twin-screw-extruder. After extrusion, the extrudate is preferably singulated, shaped and optionally coated in order to obtain the final form of administration.

In a preferred embodiment of the method according to the invention, shaping is performed with the mixture of components (A), (C), optionally (B) and optionally (D) in plasticised state. It has surprisingly been found that the extrusion of certain polymers (C), particularly of high molecular weight polyethylene oxides, produces intermediates exhibiting a certain memory effect, ie a certain recovery capacity: if the singulated extrudates are shaped at ambient temperature, eg by press-forming, forms of administration are obtained which tend to regain their original outer shape due to storage under conditions of stress, ie they return to the shaped form they had prior to shaping.

The shape of the form of administration during storage under conditions of stress, e.g. at 40°C/75% RH, may also be unstable for other reasons.

The memory effect significantly impairs the storage stability of the form of administration, since by regaining its outer shape, numerous properties of the form of administration are changed. The same applies to any changes to the outer shape due to other reasons.

It has been found that, for example, depending on the extrusion conditions, a significant expansion of the strand may occur thereby resulting in an increase in the volume of the

extrudate, ie a decrease in its density. This expansion can be compensated by subsequently press-forming the singulated extrudate at a sufficient pressure, since, under these conditions, the expansion of the material may be reversed.

If, however, the press-forming was performed at ambient temperature, the memory effect of the compressed extrudate causes it to swell and expand resulting in a significant increase in the volume of the form of administration.

It has surprisingly been found that a memory effect of this kind may be suppressed if shaping of the singulated extrudate is performed at an increased temperature, ie in the plasticised state of the mixture of components (A), (C), optionally (B) and optionally (D). Preferably, the shaping is performed at a pressure of at least 1 kN, more preferably within the range from 2 kN to 50 kN, eg by means of a tablet press. Preferably, shaping is performed at a temperature which is about 40°C, more preferably about 30°C and in particular about 25°C below the melting range of the mixture of components (A), (C), optionally (B) and optionally (D). The melting range of a given mixture may be determined by conventional methods, preferably by DSC (eg with a DSC model 2920 (TA Instruments, New Castle) and ultrahigh pure nitrogen as purge gas at a flow rate of 150 ml/min; approximate sample weight of 10-20 mg, sealed in nonhermetic aluminium pans; temperature gradient 10°C/min).

In a preferred embodiment, the outer shape of the form of administration according to the invention does not substantially change when stored for at least 12 h, preferably for at least 24 h, at 40°C and 75% RH, preferably in an open container.

In a preferred embodiment, when stored for at least 12 h, preferably for at least 24 h, at a temperature of 20°C below the melting range of the mixture of components (A), (C), optionally (B) and optionally (D), optionally at a temperature of 40°C and 75% RH, the volume of the form of administration according to the invention increases by not more than 20% or 17.5%, more preferably not more than 15% or 12.5%, still more preferably not more than 10% or 7.5%, most preferably not more than 6.0%, 5.0% or 4.0% and in particular not more than 3.0%, 2.0% or 1.0%

The form of administration according to the invention exhibits controlled release of the active ingredient. It is in this regard preferably suitable for twice daily administration to patients.

The form of administration according to the invention can comprise one or more substances (A) at least partially in a further delayed-release form, wherein delayed release may be achieved by means of conventional materials and methods known to the person skilled in the art, for example by embedding the substance in a release-delaying matrix or by applying one or more release-delaying coatings. The release of the substance must, however, be controlled such that the addition of release-delaying materials does not impair the necessary hardness.

Controlled release from the form of administration according to the invention is preferably achieved by embedding the substance in a matrix. The excipients acting as matrix materials control the release. Matrix materials may, for example, be hydrophilic, gel-forming materials, from which release proceeds mainly by diffusion, or hydrophobic materials, from which release proceeds mainly by diffusion from the pores in the matrix.

Physiologically compatible, hydrophilic materials, which are known to the person skilled in the art, may be used as matrix materials. Polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins are preferably used as hydrophilic matrix materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof are quite particularly preferably used as matrix materials.

Also preferred are matrix materials produced from hydrophobic materials, such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof. Mono- or diglycerides of C12-C30 fatty acids and/or C12-C30 fatty alcohols and/or waxes or mixtures thereof are particularly preferably used as hydrophobic materials

It is also possible to use mixtures of the above-stated hydrophilic and hydrophobic materials as matrix materials.

In addition, components (C) and the optionally present component (D), which serve to achieve the resistance to breaking of at least 400 N, which is necessary according to the invention, may furthermore themselves serve as additional matrix materials.

If the form of administration according to the invention is intended for oral administration, it may also preferably comprise a coating that is resistant to gastric juices and dissolves as a function of the pH value of the release environment. By means of this coating, it is possible to ensure that the form of administration according to the invention passes through the stomach undissolved and the active ingredient is only released in the intestines. The coating that is resistant to gastric juices preferably dissolves at a pH value of between 5 and 7.5.

Corresponding materials and methods for the delayed release of active ingredients and for the application of coatings that are resistant to gastric juices are known to the person skilled in the art, for example from "Coated Pharmaceutical Dosage Forms - Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials" by Kurt H Bauer, K Lehmann, Hermann P Osterwald, Rothgang, Gerhart, 1st edition, 1998, Medpharm Scientific Publishers. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure.

One object of the invention relates to the use of a physiologically active substance (A) as described above and/or a synthetic or natural polymer (C) as described above to produce of the form of administration according to the invention for the prevention and/or treatment of a disease with the prevention of an overdose of the physiologically active substance (A), in particular as the result of the comminution of the form of administration by exposure to mechanical action.

The invention also relates to the use of a physiologically active substance (A) as described above and/or a synthetic or natural polymer (C) as described above to produce the form of administration according to the invention to prevent an unintentional disruption, in particular cancellation, of the delayed release of the physiologically active substance (A) as the result of the comminution of the form of administration by exposure to mechanical action.

The invention further relates to the use of a form of administration according to the invention to produce a medicine for the prevention and/or treatment of a disease with the prevention of an overdose of the physiologically active substance (A), in particular as the result of the comminution of the medicine by exposure to mechanical action.

Finally, the invention relates to the use of the form of administration according to the invention to produce a medicine for the prevention and/or treatment of the disease with the prevention of an unintentional disruption, in particular cancellation of the delayed release of the physiologically active substance (A) as the result of the comminution of the medicine by exposure to mechanical action.

In this regard, said mechanical action is preferably selected from the group consisting of chewing, grinding in a mortar, pounding and the use of apparatus for the pulverisation of conventional forms of administration.

The resistance to breaking of the forms of administration according to the invention is determined according to the stated measurement method, wherein forms of administration other than tablets are also tested.

To determine the resistance to breaking of the form of administration according to the invention, forms of administration, preferably tablets, with a diameter of 10 mm and a height of 5 mm are produced.

With these forms of administration, preferably tablets, the resistance to breaking of the form of administration is determined in accordance with the method for determining the resistance to breaking of tablets published in the European Pharmacopoeia 1997, page 143, 144, method No 2.9.8. using the apparatus described below. The apparatus used for the measurement is a "Zwick Z 2.5" materials tester, Fmax = 2.5 kN with a maximum draw of 1150 mm, which should be set up with one column and one spindle, a clearance behind of 100 mm and a test speed adjustable between 0.1 and 800 mm/min together with testControl software. Measurement is performed using a pressure piston with screw-in inserts and a cylinder (diameter 10 mm), a force transducer, Fmax. 1 kN, diameter = 8 mm, class 0.5 from 10 N, class 1 from 2 N to ISO 7500-1, with manufacturer's test certificate M according to DIN 55350-18 (Zwick gross force Fmax = 1.45 kN) (all apparatus from Zwick GmbH & Co. KG, Ulm, Germany) with Order No BTC-FR 2.5 TH. D09 for the tester, Order No BTC-LC 0050N. P01 for the force transducer, Order No BO 70000 S06 for the centring device.

Figure 6 shows the measurement of the resistance to breaking of a tablet, in particular the adjustment device (6) for the tablet (4) used for this purpose before and during the

measurement. To this end, the tablet (4) is held between the upper pressure plate (1) and the lower pressure plate (3) of the force application apparatus (not shown) with the assistance of two 2-part clamping devices, which are in each case firmly attached (not shown) to the upper and lower pressure plate once the spacing (5) necessary for accommodating and centring the tablet to be measured has been established. The spacing (5) may be established by moving the 2-part clamping devices horizontally outwards or inwards in each case on the pressure plate on which they are mounted. The reference numbers used relate solely to Figure 6.

If the form of administration according to the invention is in multiparticulate form, the resistance to breaking may alternatively be determined by means of two pressure plates, such as depicted for example in Figure 7.

Figure 7 shows an upper pressure plate (10) and a lower pressure plate (11), between which the probe (12), for example a pellet, is introduced. The two pressure plates are used to apply force to the probe. The evaluation of the result of the measurement is performed in the same way as in the method described above in relation to Figure 6.

The tablets deemed resistant to breaking under a specific load include not only those that have not broken but also those that may have suffered plastic deformation under the action of the force.

The invention is explained below with reference to examples. These explanations are given merely by way of example and do not restrict the general concept of the invention.

In a first series of examples diltiazem hydrochloride, verapamil hydrochloride and carbamazepine were used as the active ingredients (substance (A)).

Example 1:

Components	Per tablet	Complete batch
Diltiazem HCl	90.0 mg	720 mg
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	154.2 mg	1233.6 mg
Total weight	244.2 mg	1.9536 g

All components were mixed in a free-fall mixer. A tabletting tool with an upper punch, lower punch and die for tablets with a diameter of 10 mm and a radius of curvature of 8 mm were heated in a heating cabinet to 80°C. The heated tool was used to press the powder mixture wherein the powder mixture was maintained for at least 15 s by clamping the tabletting tool in a vice.

The resistance to breaking of the tablets was determined in accordance with the stated method with the stated apparatus. The tablets did not crush when exposed to a force of 500 N. The tablet could not be comminuted with a hammer. This could not be achieved by means of a pestle and mortar either.

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus in accordance with Pharm Eur (paddle with sinker). The temperature of the release medium was 37°C and the rotational speed of the stirrer 50 min^{-1}. At the beginning of the investigation, each tablet was placed in a 900 ml portion of artificial gastric juice, pH 1.2. After 30 minutes, the pH value was increased to 2.3 by addition of alkali solution, after a further 90 minutes to pH 6.5 and after a further 60 minutes to pH 7.2. The quantity of active ingredient released in each case into the dissolution medium at any one time was determined by spectrophotometry at 236 nm in 2 mm measurement cells.

Time	Quantity released
30 min	12 %
240 min	43 %
480 min	63 %
600 min	71 %
720 min	77 %

Example 2:

As in Example 1, oblong tablets with a diameter of 9 mm and a longitudinal extension of 20 mm were produced with the following composition:

Components	Per tablet	Complete batch
Verapamil HCl	240.0 mg	1920 mg
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	411.4 mg	3291.2 mg
Total weight	651.4 mg	4.2112 g

The resistance to breaking of the tablets was determined in accordance with the stated method by means of the stated apparatus. The tablets did not break when exposed to an application of force of 500 N.

The in-vitro-release of the active substance was determined in a manner similar to Example 1 (UV detection at 279 nm) and was:

Time	Quantity released
30 min	6 %
240 min	20 %
480 min	30 %
600 min	35 %
720 min	39 %

Example 3:

Similarly to Example 1, round tablets with a diameter of 20 mm and the following composition were produced:

Components	Per tablet	Complete batch
Carbamazepine	600 mg	4800 mg
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	1028.5 mg	8228.0 mg
Total weight	1628.5 mg	13.028 g

The resistance to breaking of the tablets was determined according to the stated method by means of the stated apparatus. The tablets did not break when exposed to an application of force of 500 N.

The in-vitro-release of the active substance was determined in a manner similar to Example 1 (UV detection at 285 nm) and was:

Time	Quantity released
30 min	1 %
240 min	5 %
480 min	9 %
600 min	11 %
720 min	13 %

In a further series of examples, nifedipine was used as the active ingredient (substance (A)).

Example 4:

Tablets with the following composition were produced:

Raw material	Per tablet	Per batch	Proportion
Nifedipine	20 mg	2 g	10%
Polyethylene oxide 900 000 (Polyox WSR 1105 Dow Chemicals)	180 mg	18 g	90%

Nifedipine and polyethylene oxide were mixed in a free-fall mixer. The mixture was compressed on an eccentric tablet press (model EK 0, Korsch) to form circular tablets with a weight of 200 mg, a diameter of 8 mm and a radius of curvature of 8 mm. Then, the tabletting tool comprising a die, upper punch, lower punch and with a diameter of 10 mm and a radius of curvature of 8 mm was heated in a heating cabinet to 100°C. Once again, the tablets produced were pressed by means of the heated tool, wherein pressure was maintained for at least 15 seconds.

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not crush when exposed to an application of force of 500 N. The tablet could not be comminuted with a hammer and this could not be achieved by means of a pestle and mortar either.

Example 5:

Similarly to Example 4, tablets with the following composition were produced:

Raw material	Per tablet	Per batch	Proportion
Nifedipine	20 mg	2 g	10%
Polyethylene oxide 600 000 (Polyox WSR 205 Dow Chemicals)	180 mg	18 g	90%

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not crush when exposed to the application of a force of 500 N. The tablet could not be comminuted with a hammer and this could not be achieved by means of a pestle and mortar either.

Example 6:

Similarly to Example 4, tablets with the following composition were produced:

Raw material	Per tablet	Per batch	Proportion
Nifedipine	20 mg	2 g	10%
Polyethylene oxide 5 000 000 (Polyox WSR Coagulant Dow Chemicals)	180 mg	18 g	90%

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not crush when exposed to the application of a force of 500 N. The tablet could not be comminuted with a hammer and this could not be achieved by means of a pestle and mortar either

Example 7:

Similarly to Example 4, tablets with the following composition were produced:

Raw material	Per tablet	Per batch	Proportion
Nifedipine	20 mg	2 g	10%
Polyethylene oxide 100 000 (Polyox WSR N 10 Dow Chemicals)	20 mg	2 g	10%
Polyethylene oxide 5 000 000 (Polyox WSR Coagulant Dow Chemicals)	160 mg	160 g	80%

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not crush when exposed to the application of a force of 500 N. The tablet could not be comminuted with a hammer. This could not be achieved by means of a pestle and mortar either.

In a further series, tablets with tramadol HCl as the physiologically active substance (A) were produced:

Example 8:

Components	Per tablet	Complete batch
Tramadol hydrochloride	100 mg	100 g
Polyethylene oxide, NF, MFI (190°C at 21.6 kg/10 min)	200 mg	200 g

<0.5 g MW 7 000 000 (Polyox WSR 303, Dow Chemicals)		
Total weight	300 mg	300 g

Tramadol hydrochloride and polyethylene oxide powder were mixed in a free-fall mixer. A tabletting tool with upper punch, lower punch and die for tablets with a diameter of 10 mm and a radius of curvature of 8 mm was heated in a heating cabinet to 80°C. 300 mg portions of the powder mixture were pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to the application of a force of 500 N.

The tablet could not be comminuted using a hammer, nor with the assistance of a mortar and pestle.

In vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus in accordance with Pharm Eur. The temperature of the release medium was 37°C and the rotational speed of the stirrer 75 min^{-1}. At the beginning of the investigation, each tablet was placed in a 600 ml portion of artificial gastric juice, pH 1.2. After 30 minutes, the pH value was increased to 2.3 by addition of alkali solution, after a further 90 minutes to pH 6.5 and after a further 60 minutes to pH 7.2. The released quantity of active ingredient present in the dissolution medium at each point in time was determined by spectrophotometry.

Time	Quantity released
30 min	15 %
240 min	52 %
480 min	80 %
720 min	99 %

Example 9:

The powder mixture from Example 8 was heated in portions of 300 mg to 80°C and placed in the die of the tabletting tool. This was followed by pressing. The tablet has the same properties as the tablet in Example 8.

Example 10:

Raw material	Per tablet	Complete batch
Tramadol hydrochloride	50 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	100 mg	200 g
Total weight	150 mg	300 g

Tramadol hydrochloride and the components stated above were mixed in a free-fall mixer. A tabletting tool with upper punch, lower punch and die for tablets with a diameter of 7 mm was heated in a heating cabinet to 80°C. 150 mg portions of the powder mixture were each pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to the application of a force of 500 N.

The in-vitro-release of the active substance was determined as in Example 8 and was:

Time	Quantity released
30 min	15 %
240 min	62 %
480 min	88 %
720 min	99 %

Example 11:

Raw material	Per tablet	Complete batch
Tramadol hydrochloride	100 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	180 mg	180 g
Xanthan, NF	20 mg	20 g
Total weight	300 mg	300 g

Tramadol hydrochloride, xanthan and polyethylene oxide were mixed in a free-fall mixer. A tabletting tool with an upper punch, lower punch and die for tablets with a diameter of 10 mm

and a radius of curvature of 8 mm was heated to 80°C in a heating cabinet. 300 mg portions of the powder mixture were each pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to the application of a force of 500 N. The tablets did suffer a little plastic deformation.

In vitro release of the active ingredient was determined as in Example 8 and was:

Time	Quantity released
30 min	14 %
240 min	54 %
480 min	81 %
720 min	99 %

Example 12:

Raw material	Per tablet	Complete batch
Tramadol hydrochloride	50 mg	100 g
Polyethylene oxide, NF, MW 7 000 000 (Polyox WSR 303, Dow Chemicals)	90 mg	180 g
Xanthan, NF	10 mg	20 g
Total weight	300 mg	300 g

Tramadol hydrochloride, xanthan and polyethylene oxide were mixed in a free-fall mixer. A tabletting tool with a upper punch, lower punch and die for oblong tablets 10 mm in length and 5 mm in width was heated in a heating cabinet to 90°C. 150 mg portions of the powder mixture were each pressed with the heated tool, wherein pressure was maintained for at least 15 seconds by clamping the tabletting tool in a vice.

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to the application of a force of 500 N. The tablets did suffer a little plastic deformation

In vitro release of the active ingredient was determined as in Example 8 and was:

Time	Quantity released
30 min	22 %
120 min	50 %
240 min	80 %
360 min	90 %
480 min	99 %

Example 13:

A tablet with the following composition was produced as described in Example 8:

Components	Per tablet	Per batch
Oxycodon hydrochloride	20.0 mg	0.240 g
Xanthan NF	20,0 mg	0,240 g
Polyethylene oxide, NF, MFI (190°C at 21.6 kg/10 min < 0.5 g MW 7 000 000 (Polyox WSR 303 Dow Chemicals)	110.0 mg	1.320 g
Total weight	150.0 mg	1.800 g

The release of the active substance was determined as follows:

The in-vitro-release of the active substance from the tablet was determined in a paddle stirrer apparatus in accordance with Pharm Eur. The temperature of the release medium was 37°C and the rotational speed 75 rpm. The phosphate buffer, pH 6.8, described in DSP served as the release medium. The quantity of active ingredient present in the solvent at the particular time of testing was determined by spectrophotometry.

Time	Mean
0 min	0 %
30 min	17 %
240 min	61 %
480 min	90 %
720 min	101.1 %

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not break when exposed to the application of a force of 500 N.

Example 14:

Tablets of the following composition were produced:

Raw material	Per tablet	Per batch	Proportion
Tramadol HCl	100 mg	10 g	20%
Polyethylene oxide 7 000 000 (Polyox WSR 303, Dow Chemicals)	375 mg	37.5 g	75%
Carnauba wax	25 mg	2.5 g	5.0%

Tramadol hydrochloride, polyethylene oxide and carnauba wax were mixed in a free-fall mixer. The mixture was compressed on an eccentric tablet press (model EK 0, Korsch) to form tablets, the weight of the tablets was 500 mg. Round tablets with a diameter of 10 mm and a radius of curvature of 8 mm were produced. Then, the tabletting tool comprising a die, upper punch, lower punch and a diameter of 10 mm and a radius of curvature of 8 mm was heated in a heating cabinet to 130°C. Once again the tablets produced were pressed by means of the heated tool, wherein pressure was maintained for at least 15 seconds.

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not crush when exposed to the application of a force of 500 N. The tablet could not be comminuted with a hammer and this could not be achieved by means of a pestle and mortar either.

Example 15:

Similarly to Example 14, tablets with the following composition were produced:

Raw material	Per tablet	Per batch	Proportion
Tramadol HCl	100 mg	10 g	20%
Polyethylene oxide 5 000 000 (Polyox WSR Coagulant Dow Chemicals)	375 mg	37.5 g	75%
Carnauba wax	25 mg	2.5 g	5.0%

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not crush when exposed to the application of a force of 500 N. The tablet could not be comminuted with a hammer and this could not be achieved by means of a pestle and mortar either.

Example 16:

Tablets with the following composition were produced:

Raw material	Per tablet	Per batch	Proportion
Tramadol HCl	100,0 mg	1490 g	29.8%
Polyethylene oxide 7 000 000 (Polyox WSR 303, Dow Chemicals)	151.0 mg	2250 g	45.0%
Hypromellose (Metholose 90 SH 100 000 cP, ShinEtsu)	33,6 mg	500 g	10.0%
Eudragit E Granulate (Röhm)	16,8 mg	250 g	5.0%
PEG 6000	33,6 mg	500 g	10.0%
Alfa Tocopherol	0.1 mg	5 g	0.1%
Aerosil (highly disperse silicon dioxide)	0.1 mg	5 g	0.1%

50 g of the polyethylene oxide, 5 g of α-tocopherol and Aerosil was processed in a mortar to produce a homogeneous mixture. This was mixed with the further components in a free-fall mixer for 15 minutes. Subsequently, the mixture was extruded by means of a planetary-gear extruder, type BCG 10, LBB Bohle (Ennigerloh). 4 planetary spindles were used. The die diameter was 8 mm. The dosing of the powder was performed gravimetrically, 10 kg per hour. The following parameters were adjusted for extrusion: rotational speed: 50 rpm; jacket temperature: 100°C; temperature of the central spindle: 100°C; temperature of the jet heating: 120°C. After production, the extrudates were allowed to cool down to room temperature. Thereafter, they were cut into discs of the desired tablet weight. Moulding of the tablets was performed by means of an eccentric press, type EKO, made by Korsch. Circular punches (diameter of 10 mm) and a radius of curvature of 8 mm were used as the tabletting tool.

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not crush when exposed to the application of a force of 500 N. The tablet could not be comminuted with a hammer, and this could not be achieved by means of a pestle and mortar either.

The in vitro release of the active ingredient from the preparation was determined in a paddle stirrer apparatus with sinker in accordance with Pharm Eur. The temperature of the release medium was 37°C and the rotational speed of the stirrer was 75 min^{-1}. 600 ml of intestinal juice, pH 6.8, was used as the release medium. The quantity of active ingredient present in the solvent at the particular time of testing was determined by spectrophotometry.

Time	Quantity of active substance released

30 min	17 %
240 min	65 %
480 min	93 %
720 min	99 %

Example 17:

Similarly to Example 16, tablets of the following composition were produced:

Raw material	Per tablet	Per batch	Proportion
Tramadol HCl	100,0 mg	1490 g	29.8%
Polyethylene oxide 7 000 000 (Polyox WSR 303, Dow Chemicals)	151.0 mg	2250 g	45.0%
Hypromellose (Metholose 90 SH 100 000 cP of ShinEtsu)	33,6 mg	500 g	10.0%
Stamylan 1965 (SABIC® LDPE 1965T low density polyethylene)	16,8 mg	250 g	5.0%
PEG 6000	33,6 mg	500 g	10.0%
Alfa Tocopherol	0.1 mg	5 g	0.1%
Aerosil (highly disperse silicon dioxide)	0.1 mg	5 g	0.1%

The resistance to breaking of the tablets was determined with the stated apparatus in accordance with the stated method. The tablets did not crush when exposed to the application of a force of 500 N. The tablet could not be comminuted with a hammer, and this could not be achieved by means of a pestle and mortar either.

The in vitro release of the active substance from the preparation was determined in a paddle stirrer apparatus with sinker in accordance with Pharm Eur. The temperature of the release medium was 37°C and the rotational speed of the stirrer 75 min^{-1}. 600 ml of intestinal fluid, pH 6.8, were used as the release medium. The quantity of active ingredient released in each case into the dissolution medium at any one time was determined by spectrophotometry.

Time	Quantity of active substance released
30 min	17 %
240 min	62 %
480 min	85 %
720 min	94 %

Claims

1. Form of administration comprising
   - a physiologically active substance (A)
   - optionally one or a plurality of physiologically compatible excipients (B)
   - a synthetic or natural polymer (C) and
   - optionally a natural, semi-synthetic or synthetic wax (D).

wherein the form of administration has a resistance to breaking of at least 400 N, under physiological conditions, after 5 hours releases at most 99% of the substance (A) and contains neither tramadol hydrochloride nor oxycodone hydrochloride.

2. Form of administration according to claim 1, characterised in that it does not contain any psychotropically active substance.

3. Form of administration according to claim 1 or 2, characterised in that it has a resistance to breaking of at least 500 N.

4. Form of administration according to any one of the preceding claims, characterised in that it is present in the form of a tablet.

5. Form of administration according to any one of the preceding claims, characterised in that it is present in multiparticulate form, wherein the individual particles have a resistance to breaking of at least 400 N.

6. Form of administration according to claim 5, characterised in that the particles are pressed into tablets or packaged in capsules.

7. Form of administration according to any one of the preceding claims, characterised in that the polymer (C) is selected from the group polyalkylene oxide, polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, the copolymers thereof and mixtures thereof.

8. Form of administration according to any one of the preceding claims, characterised in that the polymer (C) is a polyalkylene oxide selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, the copolymers thereof, the block copolymers thereof and mixtures thereof.

9. Form of administration according to claim 7 or 8, characterised in that the polymer (C) has a viscosity-average molecular weight of at least 0.5 10^6 g/mol.

10. Form of administration according to any one of the preceding claims characterised in that it comprises a sleeve-shaped region (82) and a core (83) located therein, wherein the sleeve-shaped region (82) is connected to the core in a seamless manner and the material forming the sleeve-shaped region (82) and the material forming the core (83) substantially have the same chemical composition, but different morphology.

11. Form of administration according to claim 10, characterised in that the material forming the sleeve-shaped region (82) and the material forming the core (83) have different optical properties.

12. Form of administration according to claim 10 or 11, characterised in that the layer thickness of the sleeve-shaped region (82) is within the range of 0.1 to 4 mm.

13. Form of administration according to any one of the preceding claims, characterised in that on storage for at least 12 h at a temperature of 20°C below the melting range of the mixture of components (A), (C), optionally (B) and optionally (D), the volume of the form of administration increases by no more than 20%.

14. Form of administration according to any one of the preceding claims, characterised in that it comprises at least one wax (D) with a softening point of at least 50°C.

15. Form of administration according to claim 14, characterised in that the wax (D) is carnauba wax or beeswax.

16. Form of administration according to any one of the preceding claims characterised in that the substance (A) is present in a delayed-release matrix.

17. Form of administration according to claim 16, characterised in that the delayed-release matrix comprises the polymer (C) and/or the optionally present wax (D) as a delayed-release matrix material.

18. Form of administration according to any one of the preceding claims, characterised in that the substance (A) is a therapeutic agent, selected from the group consisting of agents for the treatment and prevention of diseases of the alimentary system and metabolism, agents for the treatment and prevention of diseases of the blood and the blood-forming organs, agents for the treatment and prevention of diseases of the cardiovascular system, dermatologicals, agents for the treatment and prevention of diseases of the genitourinary system and sex hormones, systemic hormone preparations excluding sex hormones and insulins, antiinfectives for systemic use, antineoplastic and immunomodulating agents, agents for the treatment and prevention of diseases of the musculo-skeletal system, agents for the treatment and prevention of diseases of the nervous system, antiparasitic products, insecticides and repellents; agents for the treatment and prevention of diseases of the respiratory system, agents for the treatment and prevention of diseases of the sensory organs, general diet products and therapeutic radiopharmaceuticals.

19. A method for the production of a form of administration according to any one of claims 1 to 18 comprising the following steps:,

(a) mixing of component (A), optionally (B), (C), optionally (D),

(b) optionally preforming the mixture obtained from step (a), preferably with the exposure to heat and/or force of the mixture obtained from (a), wherein the quantity of heat supplied is preferably not sufficient to heat component (C) to its softening point,

(c) hardening the mixture by exposure to heat and force, wherein the heat can be supplied during and/or before the exposure to force and the quantity of heat supplied is sufficient to heat component (C) at least to its softening point,

(d) optionally singulating the hardened mixture,

(e) optionally shaping the form of administration and

(f) optionally coating with a film coating.

20. Method according to claim 19, characterised in that in step (c) a twin-screw extruder or a planetary-gear extruder is used.

21. Method according to claim 20, characterised in that step (e) is performed in the plasticised state of the mixture of components (A), (C), optionally (B) and optionally (D).

22. Method according to any one of claims 19 to 21, characterised in that step (c) is performed under the action of ultrasound.

23. Product obtainable by a method according to any one of claims 19 to 22.

24. Use of a physiologically active substance (A) and/or a synthetic or natural polymer (C) to produce a form of administration according to any one of claims 1 to 18 for the prevention and/or treatment of a disease with the prevention of an overdose of the physiologically active substance (A), in particular due to the comminution of the form of administration by mechanical action

25. Use of a physiologically active substance (A) and/or a synthetic or natural polymer (C) to produce a form of administration according to any one of claims 1 to 18 to prevent an unintentional disruption of the delayed release of the physiologically active substance (A) due to the comminution of the form of administration by mechanical action.

26. Use of a form of administration according to any one of claims 1 to 18 to produce a medicine for the prevention and/or treatment of a disease with the prevention of an overdose of the physiologically active substance (A), in particular due to the comminution of the medicine by mechanical action.

27. Use of a form of administration according to any one of claims 1 to 18 to produce a medicine for the prevention and/or treatment of a disease with the prevention of an unintentional disruption of the delayed release of the physiologically active substance (A) due

to the comminution of the medicine by mechanical action.

28. Use according to any one of claims 24 to 27, characterised in that the mechanical action is selected from the group consisting of chewing, grinding in a mortar, pounding and the use of apparatus for the pulverisation of conventional forms of administration.

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Application number / numéro de demande: EP06/01027

Figures: 2, 3, 6, 7

Pages:

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Figure 1

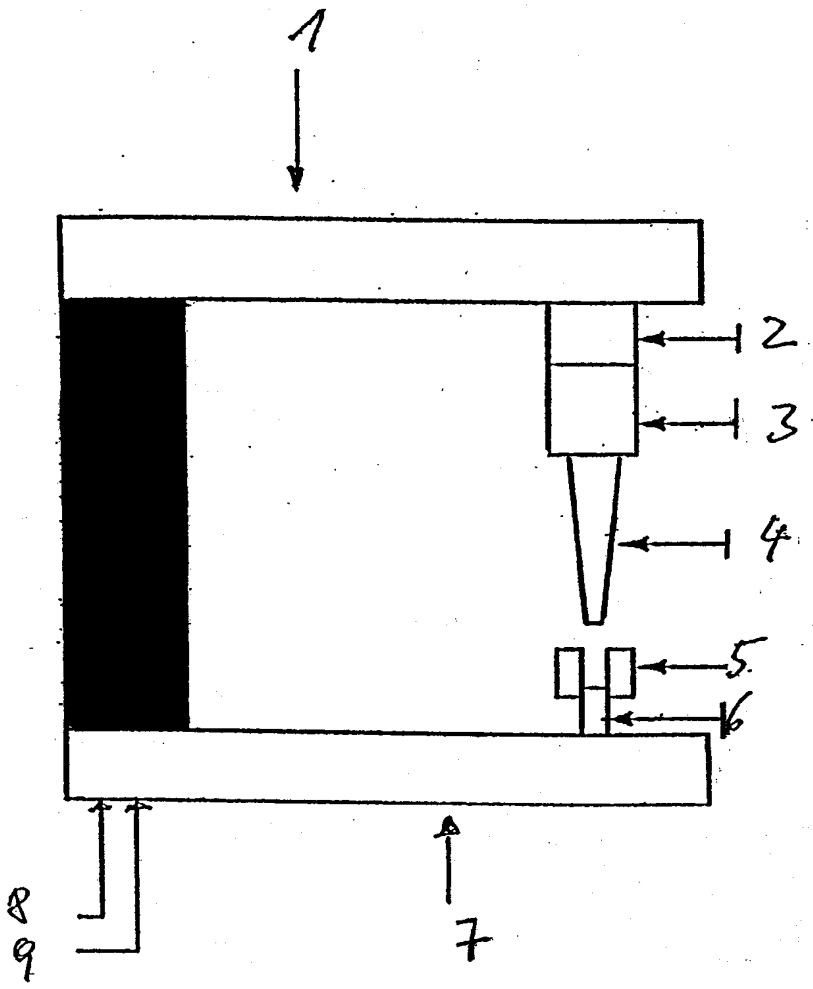

Figure 4

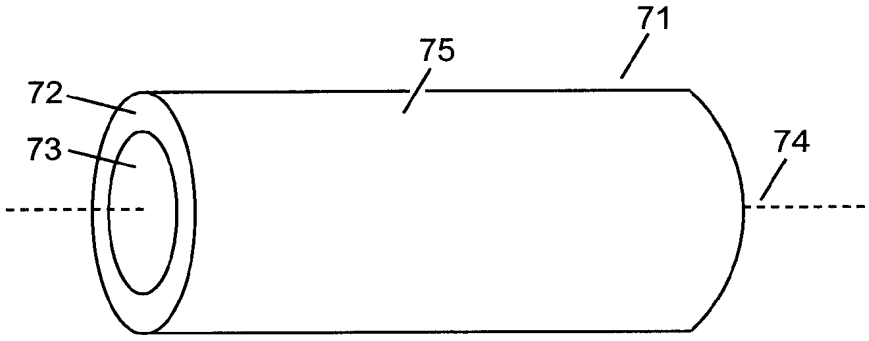

Figure 5A

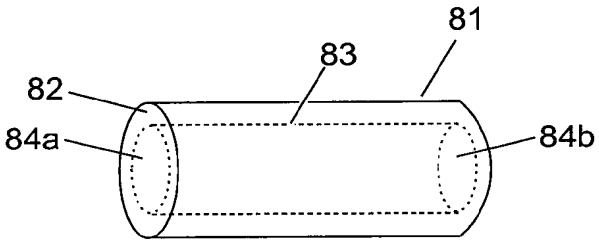

Figure 5B